Table 3B cont.

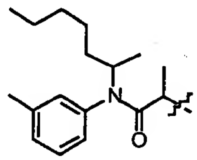
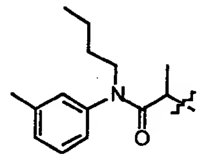
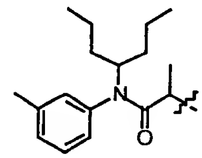
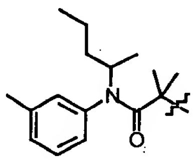
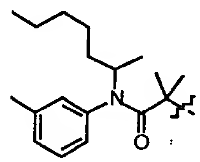
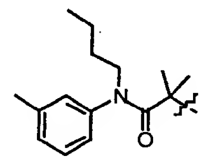
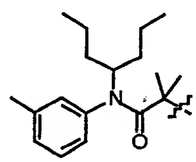
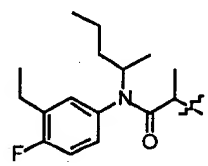
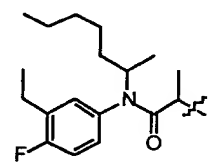
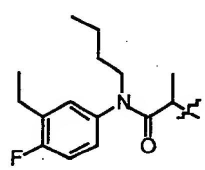
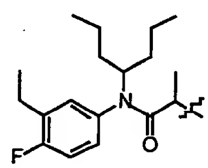
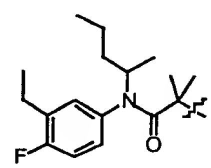
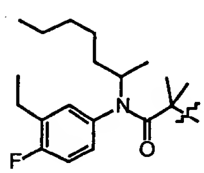
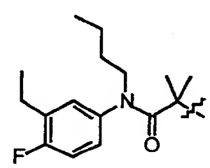
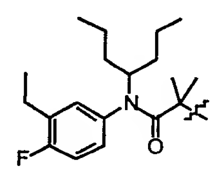
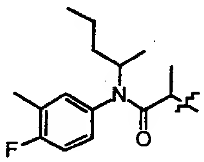
R	R	R
 583.	 584.	 585.
 586.	 587.	 588.
 589.	 590.	 591.
 592.	 593.	 594.
 595.	 596.	 597.

Table 3B cont.

R	R	R



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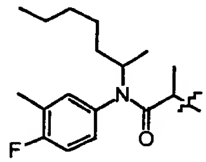

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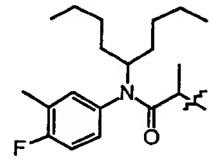

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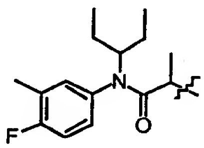

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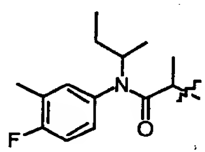

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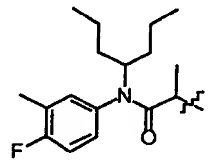

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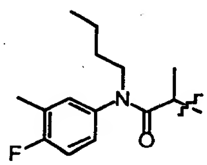
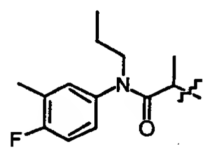
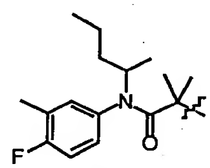


604.



605.



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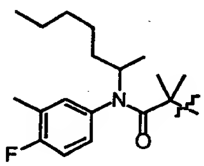

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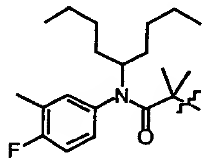

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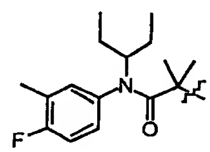

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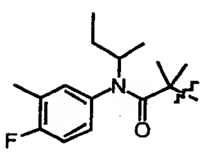

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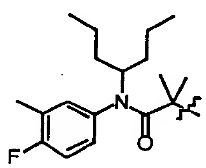

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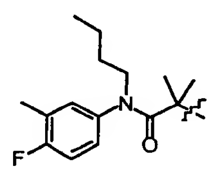
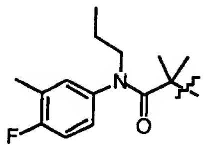


612.

Table 3B cont.

R R R



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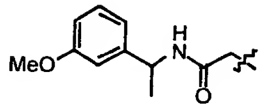

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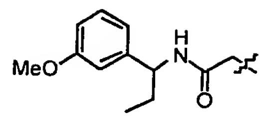

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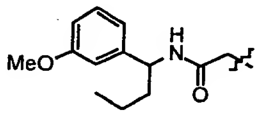

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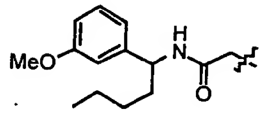
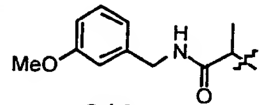
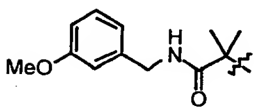


617.



618.



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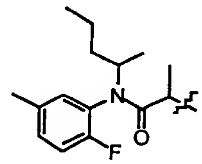
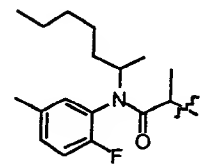


620.



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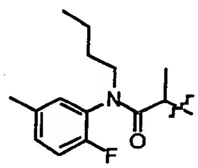

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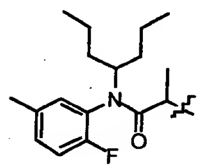

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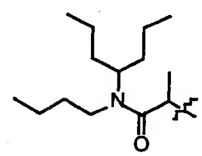
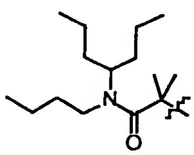
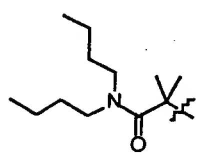


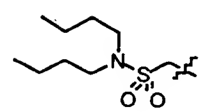
624.



625.



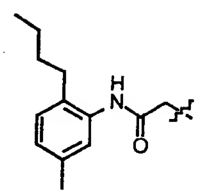
626.



627.

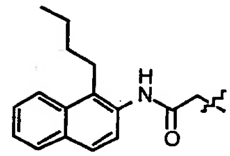
Table 3B cont.

R



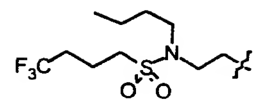
628.

R

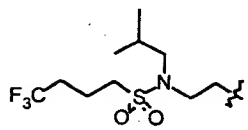


629.

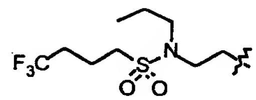
R



630.



631.



632.

Example 340

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(N-(3-methylbut-1-yl)-N-phenyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 0.85 (d, J=6 Hz, 6H), 1.25 (q, J=7 Hz, 2H), 1.42-1.56 (m, 1H), 3.43-3.85 (m, 9H), 3.88s (3), 5.95 (s, 2H), 6.80 (d, J=7 Hz, 1H), 6.86 (dd, J=9 Hz, 1H), 6.89-7.00 (m, 2H), 6.97 (d, J=1 Hz, 1H), 7.04 (d, J=9 Hz, 2H), 7.37 (d, J=9 Hz, 2H), 7.40-7.47 (m, 3H). MS (C.I.) m/e C (53.12, 53.11), H (4.63, 4.80), N (3.33, 3.28).

Example 341

trans, trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(N-butyl-N-(4-methylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 0.87 (t, J=7 Hz, 3H), 1.20-1.47 (m, 4H), 2.37 (s, 3H), 2.83 (q, J=7 Hz, 2H), 3.06-3.25 (m, 2H), 3.40-3.50 (m, 1H), 3.51-3.63 (m, 3H), 3.80 (s, 3H), 3.87 (d, J=9 Hz, 1H), 5.92 (s, 2H), 6.74 (d, J=8 Hz, 1H), 6.80-

6.86 (m, 3H), 6.89 (d, J=8 Hz, 2H), 7.04 (d, J=2 Hz, 1H), 7.12 (d, J=8 Hz, 2H), 7.19 (d, J=8 Hz, 2H). MS (DCI) m/e 545 $(M+H)^+$. Analysis calcd for $C_{32}H_{36}N_2O_6$: C, 70.57; H, 6.66; N, 5.14. Found: C, 70.20; H, 6.81; N, 5.03.

Example 342

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-propoxyphenyl)-1-(N,N-di(n-butyl)amino)carbonyl)methyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H (300MHz, $CDCl_3$) δ 7.30 (2H, d, J=9), 7.03 (1H, d, J=2), 6.83 (3H, m), 6.72 (1H, d, J=9), 5.95 (1H, d, J=2), 5.93 (1H, d, J=2), 3.88 (2H, t, J=7), 3.73 (1H, d, J=12), 3.58 (1H, m), 3.53-3.20 (4H, m), 3.10-2.90 (4H, m), 2.72 (1H, d, J=15), 1.79 (2H, q, J=8), 1.50-1.05 (8H, m), 1.02 (3H, t, J=7), 0.87 (3H, t, J=7), 0.80 (3H, t, J=7). MS (DCI/NH_3) m/e 539 $(M+H)^+$. Anal calcd for $C_{31}H_{42}N_2O_6 \cdot 0.5H_2O$: C, 67.98; H ,7.91; N, 5.11. Found: C,68.24; H, 7.70; N, 5.03.

Example 343

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-propylphenyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H (300MHz, $CDCl_3$) δ 7.31(2H, d, J=9), 7.13 (2H, d, J=9), 7.03 (1H, d, J=2), 6.84 (1H, dd, J=6, 2), 6.73 (1H, d, J=9), 5.95 (1H, d, J=2), 5.93 (1H, d, J=2), 3.76 (1H, d, J=10), 3.60 (1H, m), 3.55-3.20 (4H, m), 3.13-2.88 (4H, m), 2.75 (1H, d, J=15), 2.55 (2H, t, J=8),1.62 (2H, q, J=8), 1.50-1.00 (8H, m), 0.92 (3H, t, J=7), 0.85 (3H, t, J=7), 0.78 (3H, t, J=7). MS (DCI/NH_3) m/e 523 (MH^+). Anal calcd for $C_{31}H_{42}N_2O_5 \cdot 0.25\ H_2O$: C, 70.63; H, 8.13; N, 5.31. Found: C, 70.55; H, 8.08; N, 5.18.

Example 344

trans-trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[3-(N-propyl-N-*n*-pentanesulfonylamino)propyl]pyrrolidine-3-carboxylic acid

Using the procedures described in Example 316, the title compound was prepared. ^1H NMR (300MHz, $CDCl_3$) δ 0.85 (t, J=7Hz, 3H), 0.90 (t, J=7Hz, 3H), 1.3-1.4 (m, 4H), 1.5-1.6 (sextet, J=7, 2H), 1.65-1.8 (m, 4H), 2.05-2.15 (m, 1H), 2.43-2.56 (m, 1H), 2.72-3.1 (m, 7H), 3.27-3.4 (m, 2H), 3.5-3.6 (m, 2H), 3.80 (s, 3H), 5.95

(s, 2H), 6.73 (d, J=8Hz, 1H), 6.8-6.9 (m, 1H), 6. 85 (d, J= 9Hz, 2H), 7.02 (d, J=2Hz, 1H), 7.80 (d, J=9Hz, 2H).

Example 345

trans,trans-4-(1,2-Dihydrobenzofuran-5-yl)-2-(4-ethylphenyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H (300MHz, $CDCl_3$) δ 7.40 (3H, m), 7.22 (2H, d, J=8), 7.13 (1H, dd, J=8, 3), 6.72 (1H, d, J=9), 5.28 (1H, d, J=12), 4.55 (2H, t, J=9), 4.15 (1H, d, J=18), 4.03 (2H, m), 3.75 (2H, m), 3.40 (2H, m), 3.20 (2H, t, J=9), 3.15 (1H, m), 3.10-2.90 (2H, m), 2.63 (2H, q, J=9), 1.47 (2H, m), 1.31 (4H, m), 1.12 (3H, t, J=8), 1.10 (2H,m), 0.92 (3H, t, J=9), 0.80 (3H, t, J=9). MS (DCI/NH_3) m/e 507 ($M+H^+$). Anal calcd for $C_{31}H_{42}N_2O_4 \cdot 1.0$ TFA: C ,63.86 ; H, 6.98; N, 4.51. Found: C, 63.95; H, 7.12; N, 4.43.

Example 346

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(((N-(3-pentyl)-N-phenylamino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.93 (t, J=7.3 Hz, 3H), 0.94 (t, J=7.3 Hz, 3H), 1.33 (m, 4H), 2.72 (d, J=15.2 Hz, 1H), 2.81 (m, 1H), 3.11-3.23 (m, 2H), 3.45-3.57 (m, 2H), 3.79 (s, 3H), 3.83 (d, J=9.8 Hz, 1H), 4.54 (m, 1H), 5.92 (s, 2H), 6.73 (d, J=7.8 Hz, 1H), 6.83 (m, 3H), 6.98 (bs, 2H), 7.04 (d, J=1.7 Hz, 1H), 7.07 (2), 7.37 (m, 3H). MS (DCI) m/e 545 ($M+H^+$). Anal calcd for $C_{32}H_{33}N_2O_6 \cdot 0.35H_2O$: C, 69.76; H, 6.71; N, 5.08. Found: C, 69.72; H, 6.66; N, 4.94.

Example 347

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(((N-butyl)-N-(3-trifluoromethylphenyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.87 (t, J=6.6 Hz, 3H), 1.17-1.45 (m, 4H), 2.65 (d, J=16.5 Hz, 1H), 2.72 (m, 1H), 3.10 (t, J=9.5 Hz, 1H), 3.21-3.27 (m, 1H), 3.40 (dd, J=4.1, 9.9 Hz, 1H), 3.54 (m, 1H), 3.61-3.74 (m, 3H), 3.77 (s, 3H), 5.93 (s, 2H), 6.73-6.85 (m, 4H), 7.02 (m, 3H), 7.33 (d, J=7.5 Hz, 1H), 7.40 (s, 1H), 7.58 (t, J=7.8

Hz, 1H), 7.69 (d, J=7.5 Hz, 1H). MS (DCI) m/e 599 ($M+H^+$). Anal calcd for $C_{32}H_{33}F_3N_2O_6$: C, 64.21; H, 5.56; N, 4.68. Found: C, 64.09; H, 5.63; N, 4.57.

Example 348

trans, trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(N-propyl-N-(4-morpholinylcarbonyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.78 (t, J=7 Hz, 3H), 1.43 (q, J=7 Hz, 2H), 2.07-3.01 (m, 1H), 2.76 (dd, J=7, 9 Hz, 2H), 2.77-3.00 (m, 5H), 3.05 (3.70, J=m Hz, 11H), 3.76 (s, 3H), 5.88 (s, 2H), 6.67 (d, J=8 Hz, 1H), 6.80 (dd, J=7 Hz, 1H), 6.83-6.90 (m, 2H), 6.98 (d, J=2 Hz, 1H), 7.32-7.39 (m, 2H). MS m/e calc'd for (M+H) $C_{29}H_{39}N_3O_7$: (M+H) 540.2710,. Found (M+H) 540.2713.

Example 349

trans, trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(*cis*-2,6-dimethylpiperidin-1-yl)carbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.94 (d, J=7 Hz, 3H), 1.15d (7, 3H), 1.10-1.70 (m, 6H), 1.70-1.90 (m, 1H), 2.9. (d, J=13 Hz, 1H), 3.00-3.20 (m, 2H), 3.50 (3.70, J=m Hz, 2H), 3.79 (s, 3H), 3.80-4.00 (m, 1H), 4.10-4.65 (m, 2H), 5.95 (s, 2H), 6.70 (7.10, J=m Hz, 5H), 7.35 (m, 2H). MS m/e calc'd for $(M+H)^+$ $C_{28}H_{35}N_2O_6$: (M+H) 495.2495. Found (M+H) 495.2493.

Example 350

trans, trans-2-(4-Methoxymethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-*n*-pentanesulfonylamino)ethyl]pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared and isolated as a white solid. m.p. 57-59 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, J=7Hz, 3H), 0.90 (t, J=7Hz, 3H), 1.28-1.36 (m, 4H), 1.93 (sextet, J=7Hz, 2H), 1.72 (t, J=7Hz, 2H), 2.20-2.32 (m, 1H), 2.72-3.10 (m, 7H), 3.18-3.41 (m, 2H), 3.43 (dd, J=3Hz, J=9Hz, 1H), 3.48 (s, 3H), 3.52-3.59 (m, 1H), 3.68 (d, J=9Hz, 1H), 5.15 (s, 2H), 5.94 (s,2H), 6.73 (d, J=8Hz, 1H), 6.82 (dd, J=1Hz, J=8Hz, 1H), 6.98-7.02 (m, 3H), 7.32 (d, J=9Hz, 2H). MS (DCI/NH_3) m/e 591 $(M+H)^+$.

Example 351

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(((N-(2-butyl)-N-phenylamino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 0.79-0.89 (m, 6H), 1.14-1.21 (m, 1H), 1.25-1.40 (m, 1H), 2.64 (dd, J=4.6, 15.4 Hz, 1H), 2.76 (t, J=9.0 Hz, 1H), 3.05-3.13 (m, 2H), 3.37-3.49 (m, 2H), 3.70 (s, 3H), 3.80 (d, J=9.8 Hz, 1H), 4.53 (m, 1H), 5.83 (m, 2H), 6.65 (d, J=8.1 Hz, 1H), 6.72 (-6.76, J=m Hz, 3H), 6.87 (m, 2H), 6.95 (d, J=1.7 Hz, 1H), 7.03 (m, 2H), 7.29 (m, 3H). MS (DCI) m/e 531 $(M+H^+)$. Anal calcd for $C_{31}H_{34}N_2O_6 \cdot 0.4H_2O$: C, 69.23; H, 6.52; N, 5.21. Found: C, 69.19; H, 6.52; N, 5.03.

Example 352

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(((N-(2-propyl)-N-phenylamino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 0.99 (d, J=6.8 Hz, 6H), 2.71 (d, J=15.6 Hz, 1H), 2.84 (m, 1H), 3.13-3.18 (m, 2H), 3.45-3.58 (m, 2H), 3.79 (s, 3H), 3.88 (d, J=9.8 Hz, 1H), 4.80 (m, 1H), 5.92 (s, 2H), 6.74 (d, J=8.1 Hz, 1H), 6.83 (m, 3H), 6.96 (br s, 2H), 7.04 (d, J=1.7 Hz, 1H), 7.13 (m, 2H), 7.38 (m, 3H). MS (DCI) m/e 517 $(M+H^+)$. Anal calcd for $C_{30}H_{32}N_2O_6 \cdot 0.4H_2O \cdot 0.08CH_3CO_2C_2H_5$: C, 68.65; H, 6.28; N, 5.28. Found: C, 68.64; H, 6.35; N, 5.14.

Example 353

trans,trans-4-(4-Propoxyphenyl)-2-(4-methoxyphenyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H (300MHz, $CDCl_3$) δ 7.42 (2H, d, J=10Hz), 7.38 (2H, d, J=10Hz), 6.92 (2H, d, J=10Hz), 6.88 (2H, d, J=10Hz), 5.13 (1H, bd, J=12Hz), 4.02 (2H, m), 3.90 (2H, t, J=8Hz), 3.80 (3H, s), 3.71 (3H, m), 3.40 (2H, m), 3.19 (1H, m), 3.10-2.90 (2H, m), 1.80 (2H, m), 1.48 (2H, m), 1.29 (4H, m), 1.13 (2H, m), 1.03 (3H, t, J=8Hz), 0.92 (3H, t, J=9Hz), 0.82 (3H, t, J=9Hz). MS (DCI/NH_3) m/e 525 (MH^+). Anal calcd for $C_{31}H_{44}N_2O_5 \cdot$ 1 TFA : C, 62.06 H 7.10; N, 4.39 . Found: C, 62.43; H, 7.28; N, 4.39.

Example 354

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-((1,2,3,4-tetrahydroquinolin-1-yl)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 1.88 (quintet, J=6.5 Hz, 2H), 2.67 (t, J=6.4 Hz, 2H), 2.87 (t, J=8.6 Hz, 1H), 3.14 (m, 2H), 3.42 (dd, J=4.6, 9.7 Hz, 1H), 3.53-3.70 (m, 3H), 3.72-3.78 (m, 1H), 3.77 (s, 3H), 3.86 (d, J=9.6 Hz, 1H), 5.91 (s, 2H), 6.73 (d, J=8.1 Hz, 1H), 6.83 (m, 3H), 6.98 (d, J=1.1 Hz, 1H), 7.02-7.23 (m, 6H). MS (DCI) m/e 515 ($M+H^+$). Anal calcd for $C_{30}H_{30}N_2O_6 \cdot 0.3H_2O \cdot 0.15\ CH_3CO_2C_2H_5$: C, 68.93; H, 6.01; N, 5.25. Found: C, 68.91; H, 5.86; N, 5.19.

Example 355

trans,t rans-2-(3,4-Dimethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared and isolated as a white solid. m.p. 64-65 °C. ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.79 (t, J=7Hz, 3H), 0.88 (t, J=7Hz, 3H),1.07 (sextet, J=7Hz, 2H), 1.20-1.35 (m, 4H), 1.43 (sextet, J=7Hz, 2H), 2.83 (d, J=13.5Hz, 1H), 2.94-3.17 (m, 4H), 3.22-3.42 (m, 1H), 3.40-3.48 (m, 3H), 3.58-3.65 (m, 1H), 3.82 (s, 3H), 3.85 (s, 4H),5.92 (s, 2H), 6.73 (d, J=8Hz, 1H), 6.81 (d, J=8Hz, 1H), 6.86-6.96 (m, 3H), 7.07 (d, J=3Hz, 1H). MS (DCI/NH_3) m/e 541 $(M+H)^+$.

Example 356

trans,trans-2-(3,4-Dimethoxyphenyl)-4-(1,3-benzodioxol -5-yl)-1-[2-(N-propyl-N-*n*-pentanesulfonylamino)ethyl]pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared and isolated as a white solid. m.p. 75-86 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.75 (t, J=7Hz, 3H), 0.82 (t, J=7Hz, 3H), 1.32-1.43 (m, 6H), 1.65-1.77 (m, 2H), 3.0-3.09 (m, 4H), 3.23-3.27 (m, 2H), 3.44 (t, J=6Hz, 1H), 3.47-3.56 (m, 2H), 3.78 (d, J=9Hz, 1H), 3.83-3.93 (m, 2H), 3.87 (s, 3H), 3.92 (s, 3H), 4.63 (d, J=13Hz, 1H), 5.97 (s, 2H), 6.82 (d, J=7Hz, 1H), 6.93 (d, J=7Hz, 1H), 7.06 (d, J=7Hz, 1H), 7.08 (d, J=3Hz, 1H), 7.16 (dd, J=3Hz, J=7Hz, 1H), 7.27 (d, J=3Hz, 1H). MS (DCI/NH_3) m/e 591 $(M+H)^+$.

Example 357

trans,trans-2-(3,4-Dimethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-*n*-hexanesulfonylamino)ethyl]pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared and isolated as a white solid. m.p. 65-66 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, J=7Hz, 3H), 0.89 (t, J=7Hz, 3H), 1.23-1.48 (m, 6H), 1.43 (sextet, J=7Hz, 2H), 1.72 (sextet,J=7Hz, 2H), 2.25-2.35 (m, 1H), 2.73-3.10 (m, 7H), 3.19-3.32 (m, 2H), 3.45 (dd, J=3Hz, J=9Hz, 1H), 3.53-3.59 (m, 1H), 3.68 (d, J=9Hz, 1H),3.87 (s, 6H), 5.95 (s, 2H), 6.74 (d, J=8Hz, 1H), 6.79-6.86 (m, 2H), 6.92-6.97 (m, 2H), 7.02 (s, 1H). MS (DCI/NH_3) m/e 605 $(M+H)^+$.

Example 358

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(phthalimido)ethyl]-pyrrolidine-3-carboxylic acid

The compound of Example 1C (250 mg), N-bromoethylphthalimide (206 mg), and diisopropylethylamine (175 mg) were dissolved in 1 mL of acetonitrile and heated for 2.5 hours at 95 °C. Toluene was added, and the mixture was washed with $KHCO_3$ solution. The solution was dried (Na_2SO_4) and concentrated. The crude product was purified by chromatography on silica gel eluting with 3:1 EtOAc-hexane to give 216 mg of an intermediate ethyl ester which was hydrolyzed by the method of Example 1D to give 130 mg of the title compound as a white powder. ^1H NMR (300 MHz, $CDCl_3$) δ 3.12-3.26 (m, 2H), 3.60-3.75 (m, 2H), 3.70 (s, 3H), 3.98-4.12 (m, 2H), 4.45-4.55 (m, 1H), 4.69 (d, J=9Hz, 1H), 4.76-4.88 (m, 1H), 5.96 (s, 2H), 6.55 (d, J=8Hz, 1H), 6.60-6.70 (m, 3H), 6.79 (d, J=8Hz, 1H), 7.05-7.45 (m, 5H), 7.75 (d, J=7Hz, 1H).

Example 359

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(((N-(2-pentyl)-N-phenylamino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 0.86-0.98 (m, 6H), 1.17-1.22 (m, 1H), 1.23-1.41 (m, 3H), 2.70 (dd, J=11.2, 15.3 Hz, 1H), 2.83 (m, 1H), 3.10-3.21 (m, 2H), 3.45-3.60 (m, 2H), 3.79 (s, 3H), 3.86 (m, 1H), 4.74 (m, 1H), 5.91 (m, 2H), 6.73 (dd, J=1.1, 7.7 Hz, 3H), 6.82 (m, 2H), 7.04-7.14 (m, 3H), 7.36 (m, 3H). MS (DCI) m/e 545 ($M+H^+$). Anal calcd for $C_{32}H_{36}N_2O_6 \cdot 0.25\ CH_3CO_2C_2H_5$: C, 69.95; H, 6.76; N, 4.94. Found: C, 70.03; H, 6.54; N, 4.78.

Example 360

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(N-butyl-N-(2-naphthyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 0.83 (t, J=7 Hz, 3H), 1.23-1.39 (m, 4H), 1.40-1.55 (m, 3H), 2.60-2.72 (m, 2H), 3.00-3.80 (m, 5H), 3.66 (s, 3H), 5.87 (s, 2H), 6.39 (d, J=9 Hz, 2H), 6.74-6.85 (m, 3H), 7.17 (d, J=2 Hz, 1H), 7.40 (dd, J=8 Hz, 1H), 7.52-7.62 (m, 3H), 7.80-7.90 (m, 1H), 7.90-8.00 (m, 2H). MS (DCI) m/e 581 $(M+H)^+$. Analysis calcd for $C_{35}H_{36}N_2O_6 \cdot 0.3\ H_2O$: C, 71.73; H, 6.29; N, 4.78. Found: C, 71.74; H, 6.26; N, 4.72.

Example 361

trans,trans-2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-*n*-pentanesulfonylamino)ethyl]pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared and isolated as a white solid. m.p. 53-54 °C. ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.79 (t, J=7Hz, 3H), 0.89 (t, J=7Hz, 3H), 1.03 (t, J=7Hz, 3H), 1.24-1.34 (m, 4H), 1.43 (sextet, J=7Hz, 2H), 1.67-1.75 (m, 2H), 1.80 (sextet, 2H), 2.23-2.33 (m, 1H), 2.72-2.93 (m, 5H), 3.05 (septet, J=7Hz, 2H), 3.15-3.35 (m, 2H), 3.42 (d, J=9Hz, 1H), 3.54-3.62 (m, 1H), 3.67 (d, J=9Hz, 1H), 4.90 (t, J=7Hz, 2H), 5.95 (s, 2H), 6.73 (d, J=8Hz, 1H), 6.85 (d, J=8Hz, 2H), 7.02 (s, 1H), 7.32 (d, J=8Hz, 2H). MS (DCI/NH_3) m/e 589 $(M+H)^+$.

Example 362

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-((2-methylindolin-1-yl)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ mixture of indole C_2 diastereomers, 0.95 (m, 1.5 (CH_3)), 1.05 (d, 6.3H, 1.5 (CH_3)), 2.62 (m, 1H), 3.01 (m, 2H), 3.14-3.25 (m, 1H), 3.37-3.52 (m, 1.5H), 3.56-3.80 (m, 2H), 3.65 (s, 1.5 (CH_3O)), 3.76 (s, 1.5 (CH_3O)), 3.93 (m, 0.5H), 4.05-4.13 (m, 0.5H,), 4.42 (m, 0.5H), 4.65-4.74 (m, 1H), 5.91 (m, 2H), 6.72 (d, J=8.1 Hz, 0.5H), 6.75 (m, 0.5H), 6.85 (m, 2H), 6.92 (d, J=8.5 Hz, 1H), 7.00-7.06 (m, 2H), 7.14 (t, J=7.7 Hz, 1H), 7.21 (t, J=6.6 Hz, 1H), 7.38 (m, 2H), 7.99 (m, 1H). MS (DCI) m/e 515 ($M+H^+$). Anal calcd for $C_{30}H_{30}N_2O_6 \cdot 0.35H_2O \cdot 0.3\ CH_3CO_2C_2H_5$: C, 68.47; H, 6.10; N, 5.12. Found: C, 68.46; H, 5.97; N, 5.07.

Example 363

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(2-hydroxy-3-propylhex-1-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 1.06 (m, 6H), 1.26-1.60 (m, 9H), 3.16 (dd, J=10.9, 12.6 Hz, 1H), 3.18 (d, J=11 Hz, 1H), 3.44 (d, J=2.0 Hz, 1H), 3.61 (t, J=11 Hz, 1H), 3.73 (t, J=11.0 Hz, 1H), 3.85 (m, 1H), 3.96-4.17 (m, 2H), 4.02 (s, 1.5 (CH_3O diastereomer)), 4.03 (s, 1.5 (CH_3O diastereomer)), 6.15 (s, 2H), 7.01 (d, J=8.1 Hz,

0.5H), 7.00 (d, J=8.1 Hz, 0.5H), 7.10 (m, 1H), 7.23 (m, 3H), 7.77 (m, 2H). MS (DCI.) m/e 484 ($M+H^+$). Anal calcd for $C_{28}H_{37}NO_6 \cdot 0.33\ H_3PO_4$: C, 65.34; H, 7.44; N, 2.72. Found: C, 65.30; H, 7.40; N, 2.60.

Example 364

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(((N-(4-heptyl)-N-(3,4-dimethoxybenzyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ1:1 mixture of rotamers, 0.61 (t, J=7.1 Hz, 1.5H), 0.72 (7.3, 1.5H), 0.76 (t, J=7.1, 1.5, 0.83, t, 7.3 Hz, 1.5H), 1.05-1.60 (m, 8H), 2.84-3.10 (m, J=2.5, 3.18, t, 9.7 Hz, 0.5H), 3.41-3.52 (m, 2H), 3.47-3.69 (m, 2H), 3.66 (s, 1.5H), 3.73 (s, 1.5H), 3.77 (s, 1.5H), 3.78 (s, 1.5H), 3.79 (s, 1.5H), 3.86 (d, J=9.8 Hz, 0.5H), 4.19 (d, J=17.7 Hz, 0.5H), 4.29 (d, J=15.2 Hz, 0.5H), 4.40-4.49 (m, 0.5H), 4.47 (d, J=15.3 Hz, 0.5H), 4.60 (d, J=17.6 Hz, 0.5H), 5.93 (m, 2H), 6.46 (dd, J=1.7, 8.2 Hz, 0.5H), 6.52 (d, J=2.0 Hz, 0.5H), 6.74 (m, 2.5H), 6.80 (s, 1H), 6.83-6.88 (m, 1H), 6.92 (m, 1.5H), 7.03 (dd, J=1.7, 6.8 Hz, 1H), 7.19 (m, 1H), 7.36 (m, 1H). MS (DCI) m/e 647 ($M+H^+$). Anal calcd for $C_{37}H_{46}N_2O_8$: C, 68.71; H, 7.17; N, 4.33. Found: C, 68.41; H, 7.26; N, 4.11.

Example 365

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-((indolin-1-yl)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ2.97 (dd, J=8.1, 9.5 Hz, 1H), 3.10 (t, J=8.1 Hz, 2H), 3.16-3.22 (m, 2H), 3.51-3.68 (m, 3H), 3.73 (m, 3H), 3.83-4.05 (m, 3H), 5.90 (m, 2H), 6.73 (d, J=8.1 Hz, 1H), 6.86 (m, 3H), 6.99 (dt, J=1.1, 7.4 Hz, 1H), 7.08 (d, J=0.7 Hz, 1H), 7.11 (m, 1H), 7.18 (d, J=7.1 Hz, 1H), 7.38 (d, J=8.5 Hz, 2H), 8.02 (8.1, 1H). MS (C.I.) m/e 501 ($M+H^+$). Anal calcd for $C_{29}H_{28}N_2O_6 \cdot 0.5\ H_2O \cdot 0.15\ CH_3CO_2C_2H_5$: C, 68.01; H, 5.82; N, 5.36. Found: C, 68.03; H, 5.65; N, 5.25.

Example 366

trans, trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(N-butyl-N-(2-chlorophenyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ0.89 (dt, J=7 Hz, 3H), 1.23-1.51 (m, 4H),

2.52-4.00 (m, 8H), 3.78 (d, J=6 Hz, 3H), 5.92 (d, J=6 Hz, 2H), 6.70-6.87 (m, 4H), 7.02-7.21 (m, 4H), 7.27-7.52 (m, 3H). MS (DCI) m/e 565 $(M+H)^+$. Analysis calcd for $C_{31}H_{32}N_2O_6Cl \cdot 0.6H_2O$: C, 64.66; H, 5.99; N, 4.86. Found: C, 64.59; H, 6.00; N, 4.64.

Example 367

trans,trans-2-(4-Methoxphenyl)-4-(1,3-benzodioxol-5-yl)-1-(3,4,5-trimethoxybenzyl)pyrrolidine-3-carboxylic acid

The compound resulting from Example 1C (0.25 g) was reacted with 0.169 g of 3,4,5-trimethoxybenzyl chloride and 0.175 g of diisopropylethylamine in 1 mL of acetonitrile for 2 hours at room temperature. The resulting ester was isolated and then hydrolyzed by the method of Example 1D to give 0.193 g of the title compound. m.p. 108-110 °C. ^1H NMR (300 MHz, $CDCl_3$) δ2.75 (t, J=9Hz, 1H), 2.95-3.05 (m, 2H), 3.20 (d, J=11 Hz, 1H), 3.45-3.55 (m, 1H), 3.7-3.8 (m, 2H), 3.84 (s, 3H), 5.95 (dd, J=2Hz, 6Hz, 2H), 6.55 (s, 2H), 6.70 (d, J=8Hz, 1H), 6.30-6.35 (m, 1H), 6.90 (d, J=9Hz, 2H), 7.13 (d, J=2Hz, 1H), 7.43 (d, J=9Hz, 2H).

Example 368

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(N-butyl-N-(3-chlorophenyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 0.89 (t, J=7 Hz, 3H), 1.20-1.42 (m, 4H), 3.42-3.87 (m, 9H), 3.9 (s, 3H), 5.96 (s, 2H), 6.75 (7.10, J=m Hz, 7H), 7.33-7.50 (m, 4H). MS (C.I.) m/e 565(M+H). Analysis calcd for $C_{31}H_{33}N_2O_6Cl \cdot 1.0CF_3COOH$: C, 58.37; H, 5.05; N, 4.13. Found: C, 58.41; H, 4.99; N, 4.08.

Example 369

trans,trans-2-(4-Methoxphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(di-*n*-butylamino)pyrimidin-4-yl]pyrrolidine-3-carboxylic acid

The compound resulting from Example 1C (0.25 g) was reacted with 0.11 g of 2,4-dichloropyrimidine and 0.175 g of diisopropylethylamine in 1 mL of acetonitrile for 2 hours at room temperature to give 0.218 g of ethyl 2-(4-methoxphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-chloro-4-pyrimidyl)-pyrrolidine-3-carboxylate. This compound was reacted with 1 mL of dibutylamine in 2 mL of toluene at 125 °C for 17 hours. The resulting ethyl ester was hydrolyzed by the method of Example 1D to give 0.142 g of the title comopund as a white powder. ^1H NMR (300 MHz, $CDCl_3$) δ0.75-0.90

(broad, 6H), 1.1-1.3 (br, 4H), 1.35-1.55 (br, 4H), 3.05 (m, 1H), 3.3-3.5 (br, 2H), 3.55-3.67 (m, 2H), 3.75 (s, 3H), 4.6 (br, 1H), 5.2 (br, 1H), 5.45 (br, 1H), 5.87 (s, 2H), 6.3 (br, 1H), 6.67 (d, J=8Hz, 1H), 6.7-6.85 (m, 4H), 7.10 (d, J=9Hz, 2H).

Example 370

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(((N-(2-methylbut-2-yl)-N-phenylamino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.90 (t, J=7.5 Hz, 3H), 1.12 (s, 3H), 1.14 (s, 3H), 2.06 (q, J=7.5 Hz, 2H), 2.73 (d, J=15.3 Hz, 1H), 2.91 (t, J=9.5 Hz, 1H), 3.11 (d, J=15.6 Hz, 1H), 3.21 (t, J=8.8 Hz, 1H), 3.50-3.61 (m, 2H), 3.80 (s, 3H), 4.00 (d, J=10.2 Hz, 1H), 5.91 (s, 2H), 6.74 (d, J=7.8 Hz, 1H), 6.85 (m, 3H), 6.93 (m, 1H), 6.98 (m, 1H), 7.03 (d, J=1.7 Hz, 1H), 7.17 (m, 2H), 7.36 (m, 3H). MS (DCI) m/e 545 ($M+H^+$). Anal calcd for $C_{32}H_{36}N_2O_6$: C, 70.57; H, 6.66; N, 5.14. Found: C, 70.17; H, 6.53; N, 4.97.

Example 371

trans,trans-2-(4-Ethylphenyl)-4-(5-indanyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H (300MHz, $CDCl_3$) δ 7.25 (3H, m), 7.21 (1H, d, 3Hz), 7.17 (3H, m), 3.80 (1H, d, 10Hz), 3.65 (1H, ddd, 6, 5, 3Hz), 3.4 (4H, m), 3.10 (2H, m), 2.98 (2H, m), 2.88 (5H, m), 2.79 (1H, d, 16Hz), 2.62 (2H, q, 7Hz), 2.05 (2H, m), 1.42 (2H, m), 1.32 (1H, m), 1.21 (3H, t, 7Hz), 1.05 (2H, sext, 7Hz), 0.87 (3H, t, 7Hz), 0.79 (3H, t, 7Hz). MS (DCI, NH_3) m/e 505 ($M+H^+$). Anal calcd for $C_{32}H_{44}N_2O_3$: C, 76.15; H, 8.79; N 5.55. Found: C, 75.96; H, 8.75; N, 5.36.

Example 372

trans, rans-2-(3,4-Difluorophenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared and isolated as a white solid. m.p. 62-63 °C. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 0.83 (t, J=7Hz, 3H), 0.88 (t, J=7Hz, 3H), 1.13 (sextet, J=7Hz, 2H),1.20-1.32 (m,3H), 1.36-1.49 (m,3H), 2.85-2.93 (m,2H), 2.98-3.23 (m, 4H), 3.36-3.45 (m, 3H), 3.58-3.66 (m 1H), 3.94 (d, J=8Hz, 1H), 5.93 (s, 2H), 6.72 (d, J=7.5Hz, 1H), 6.84 (dd,

J=1Hz, J=7.5Hz, 1H), 6.98 (d, J=7.5Hz, 1H), 7.08-7.15 (m, 2H), 7.22-7.28 (m, 1H). MS (CDI/NH_3) m/e517 $(M+H)^+$.

Example 373

trans,trans-2-(3,4-Difluorophenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-*n*-pentanesulfonylamino)ethyl]pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared and isolated as a white solid. m.p. 71-72 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, J=7Hz, 3H), 0.90 (t, J=7Hz, 3H), 1.25-1.38 (m, 4H), 1.46 (sextet, J=7Hz, 2H), 1.74 (quintett, J=7Hz, 2H), 2.26-2.36 (m, 1H), 2.72-2.95 (m, 5H), 2.98-3.12 (m, 2H), 3.15-3.34 (m, 2H), 3.45 (dd, J=3Hz, J=9Hz, 1H), 3.53-3.60 (m, 1H), 3.71 (d, J=9Hz, 1H), 5.96 (s, 2H), 6.75 (d, J=9Hz, 1H), 3.82 (dd,, J=2Hz, J=9Hz, 1H), 5.96 (d, J=2Hz, 1H), 7.09-7.18 (m, 2H), 7.23-7.34 (m, 1H). MS (CDI/NH_3) m/e567 $(M+H)^+$.

Example 374

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(ethoxymethyl)-1-(((N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. TLC (10% MeOH-CH_2Cl_2) R_f = 0.53. ^1H NMR ($CDCl_3$, 300 MHz, rotameric forms) δ 0.70 (t, J=7Hz), 0.80 (t, J=7Hz) and 0.96-1.04 (m, 6H total), 1.04-1.75 (m, 11H), 1.34-1.53 (br m, 4H), 2.65 (AB) and 2.80-3.08 (m, 2H total), 3.10-3.82 (br m, 12H), 4.03 (m) and 4.22-4.45 (br m, 2H total), 5.90 (s) and 5.91 (s, 2H total), 6.65-6.84 (m) and 6.93 (m) and 6.99 (m, 3H total). MS (FAB) m/e 463 $(M+H)^+$. Anal calcd for $C_{25}H_{38}N_2O_6 \cdot 1.5\ H_2O$: C, 61.33; H, 8.44; N, 5.72. Found: C, 61.28; H, 7.78; N, 5.62.

Example 375

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(*n*-butyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared and isolated as a colorless wax. TLC (10% MeOH-CH_2Cl_2) R_f = 0.37. ^1H NMR ($CDCl_3$, 300 MHz, rotameric forms) δ 0.71 (t, J=7Hz) and 0.77-1.05 (m, 9H total), 1.05-1.20 (m, 2H), 1.20-1.72 (br m, 13H), 2.48-2.52 (m, 1H), 2.87-3.00 (m, 1H), 3.05-3.60 (m, 5H), 3.60-3.80 (br m, 2H), 3.88-4.05 (br m, 1H), 4.28 (br d,

J=15Hz, 1H total), 5.90 (s) and 5.92 (s, 2H total), 6.67-6.82 (m, 3H total). MS (FAB) m/e 461 $(M+H)^+$. Anal calcd for $C_{26}H_{40}N_2O_5 \cdot 1.75\ H_2O$: C, 63.45; H, 8.90; N, 5.69. Found: C, 63.18; H, 8.22; N, 5.60.

Example 376

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(2-methylbutyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared and isolated as a colorless glass. TLC (10% MeOH-CH_2Cl_2) R_f = 0.49. ^{1}H NMR ($CDCl_3$, 300 MHz, rotameric forms and mixture of diastereomers) δ 0.69 (br t, J=7Hz) and 0.75-2.15 (several br m, approx. 26H total), 2.48-2.65 (br m, 1H), 2.87-3.01 (br m, 1H), 3.06-3.82 (br m, 7H), 3.90-4.40 (br m, 2H), 5.90 (s) and 5.92 (s, 2H total), 6.67-6.90 (m, 3H total). MS (FAB) m/e 475 $(M+H)^+$.

Example 377.

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(3-methylbutyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. TLC (10% MeOH-CH_2Cl_2) R_f = 0.41. ^{1}H NMR ($CDCl_3$, 300 MHz, rotameric forms) δ 0.73 (t, J=7Hz) and 0.77-1.05 (m, 12H total), 1.07-1.75 (m, approx. 14H plus H_2O), 2.48-2.63 (m, 1H), 2.87-3.05 (m, 1H), 3.05-3.60 (several br m, 5H), 3.62-4.02 (br m, 2H), 4.29 (br d, J=15Hz, 1H), 5.89 (s) and 5.93 (s, 2H total), 6.65-6.90 (m, 3H total). MS (FAB) m/e 475 $(M+H)^+$.

Example 378

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-((N-methyl-N-propylamino)sulfonyl)amino)ethyl]pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared and isolated as a white solid. m.p. 58-59 °C. ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.78 (t, J=7Hz, 3H), 0.90 (t, J=7Hz, 3H), 1.27 (sextet, J=7Hz, 2H), 1.48 (m, 4H), 2.22-2.30 (m, 1H), 2.62 (s, 3H), 2.68-2.78 (m, 1H), 2.84-3.03 (m, 5H), 3.08-3.31 (m, 3H),3.39 (dd, J=3Hz, J=9Hz,1H), 3.50-3.58 (m, 1H), 3.63 (d, J=9Hz, 1H),3.79 (s, 3H), 5.95 (s, 2H), 3.73 (d, J=8Hz, 1H), 6.83 (dd, J=2Hz, J=8Hz, 1H), 3.87 (d, J=9Hz, 2H), 7.01 (d, J=2Hz, 1H), 7.33 (d, J=9Hz, 2H). MS (DCI/NH_3) m/e 576 $(M+H)^+$.

Example 379

trans,trans-2,4-Di(3,4-difluorophenyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300MHz, $CDCl_3$) δ 7.35 (2H, m), 7.18 (4H, m), 4.87 (1H, d, J=12), 4.00-3.60 (5H, m), 3.60-3.10 (3H, m), 3.10-2.90 (2H, m), 1.45 (2H, m), 1.29 (4H, m), 1.15 (2H, m), 0.91 (3H, t, J=9), 0.83 (3H, t, J=9). MS (DCI/NH_3) m/e 509 ($M+H^+$). Anal calcd for $C_{27}H_{32}F_4N_2O_3$· 0.75 TFA: C, 57.62; H, 5.56; N, 4.72. Found: C, 57.72; H, 5.67; N, 4.66.

Example 380

trans,trans-4-(3,4-Dimethylphenyl)-2-(4-methoxyphenyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (2H, d, J=9), 7.25 (1H, bs), 7.18 (1H, dd, J=8, 3), 7.11 (1H, d, J=9), 6.90 (2H, d, J=10), 5.48 (1H, d, J=12), 4.26 (1H, d, J=18), 4.16 (2H, m), 3.83 (2H, m), 3.81 (3H, s), 3.56 (1H, bd, J=18), 3.37 (1H, m), 3.20 (1H, m), 2.96 (2H, m), 2.24 (3H, s), 2.22 (3H, s), 1.47 (2H, m), 1.27 (4H, m), 1.10 (2H, m), 0.93 (3H, t, J=9), 0.81 (3H, t, J=9). MS (DCI/NH_3) m/e 495 ($M+H^+$). Anal calcd for $C_{30}H_{42}N_2O_4$· 1.25 TFA: C, 61.26; H, 6.84; N, 4.40. Found: C, 61.16; H, 7.05; N, 4.38.

Example 381

trans,trans-2,4-Di(3-fluoro-4-methoxyphenyl)-1-(N,N-di(n-butyl)aminocarbony)methyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300MHz, $CDCl_3$) δ 7.20 (2H, m), 7.17 (2H, m), 6.93 (2H, m), 5.48 (1H, m), 4.26 (1H, m), 4.16 (2H, m), 3.83 (2H, m), 3.87 (6H, s), 3.56 (1H, m), 3.37 (1H, m), 3.20 (1H, m), 2.96 (2H, m), 1.47 (2H, m), 1.27 (4H, m), 1.10 (2H, m), 0.93 (3H, t, J=9), 0.81 (3H, t, J=9). MS (DCI/NH_3) m/e 533 ($M+H^+$). Anal calcd for $C_{29}H_{38}F_2N_2O_5$· 0.75 H_2O: C, 63.78; H, 7.29; N, 5.13. Found: C, 63.77; H, 7.08; N, 4.99.

Example 382

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(((N-(2-pentyl),N-(3-methylphenyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.90 (m, 3H), 0.95 (t, J=7.3 Hz, 3H), 1.13-1.37 (m, 4H), 2.30 (s, 3H), 2.34 (s (CH_3 rotamer)), 2.73-2.91 (m, 2H), 3.17-3.26 (m, 2H), 3.32-3.62 (m, 2H), 3.77-4.08 (m, 1H), 3.80 (s, 3H), 4.71 (m, 1H), 5.92 (m, 2H), 6.61-6.84 (m, 6H), 7.04-7.16 (m, 3H), 7.23-7.29 (m, 2H). MS (DCI) m/e 559 $(M+H^+)$. Anal calcd for $C_{33}H_{38}N_2O_6 \cdot 0.35\ H_2O \cdot 0.05\ CH_3CO_2C_2H_5$: C, 70.03; H, 6.92; N, 4.92. Found: C, 70.08; H, 6.82; N, 4.95.

Example 383

trans, trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(N-butyl-N-(1-naphthyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.87 (t, J=7 Hz, 3H), 1.20-1.40 (m, 2H), 1.40-1.60 (m, 2H), 2.42-2.80 (m, 2H), 2.85-4.00 (m, 6H), 3.77 (d, J=1.5 Hz, 3H), 4.05-4.20 (m, 1H), 5.94 (d, J=2 Hz, 2H), 6.6 (dd, J=9, 10 Hz, 1H), 6.70-6.85 (m, 4H), 6.95-7.02 (m, 2H), 7.17 (dd, 8H, 1/2), 7.25 (dd, 8H, 1/2), 7.38-7.60 (m, 4H), 7.87-8.00 (m, 2H). MS (E.S.I.) m/e (M+H) 581. Analysis calcd for $C_{35}H_{36}N_2O_6 \cdot 1.4\ H_2O$: C, 69.38; H, 6.45; N, 4.62. Found: C, 69.36; H, 6.07; N, 4.41.

Example 384

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-phenyl-N-*n*-hexanesulfonylamino)ethyl]pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared and isolated as a tan solid. m.p. 67-68 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.88 (t, J=7Hz, 3H), 1.25-1.40 (m, 6H), 1.73 (quintet, J=7Hz, 2H), 2.13-2.23 (m, 1H), 2.64-2.88 (m, 3H), 3.02 (sextet, J=8Hz, 2H), 3.44-3.53 (m, 2H), 3.58 (d, J=9Hz, 1H), 3.56-3.75 (m, 1H), 3.78 (s, 3H), 3.88-3.98 (m, 1H), 5.93 (s, 2H), 6.72 (d, J=9Hz, 1H), 5.78-5.84 (m, 3H), 6.96 (d, J=2Hz, 1H), 7.20 (d, J=9Hz, 2H), 7.27-7.36 (m, 5H). MS (DCI/NH_3) m/e 609 $(M+H)^+$.

Example 385

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(2-methyl-1,2,3,4-tetrahydroquinolin-1-yl)carbonylmethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 1.03 (m, 3H), 1.10-1.45 (m, 1H), 2.10-2.85 (m, 4H), 2.90-4.00 (m, 7H), 3.76 (s, 1.5H), 3.77 (s, 1.5H, isomer), 5.90 (m, 2H), 6.70-7.40 (m, 11H). MS (DCI) m/e 529 $(M+H)^+$. Analysis calcd for $C_{31}H_{32}N_2O_6 \cdot 0.3\ H_2O$: C, 69.73; H, 6.15; N, 5.25. Found: C, 69.74; H, 6.10; N, 5.01.

Example 386

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(3-butyl-hept-2-en-1-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 0.86 (t, J=7.0 Hz, 3H), 0.90 (t, J=7.0 Hz, 3H), 1.20-1.41 (m, 8H), 1.95-2.06 (m, 4H), 3.24 (d, J=11.0 Hz, 1H), 3.51-3.59 (m, 3H), 3.60-3.71 (m, 1H), 3.77-3.84 (m, 1H), 3.81 (s, 3H), 4.45 (d, J=11.0 Hz, 1H), 5.52 (t, J=7.4 Hz, 1H), 5.93 (s, 2H), 6.77 (d, J=8.1 Hz, 1H), 6.87 (dd, J=1.8, 8.1 Hz, 1H), 6.99 (m, 3H), 7.46 (m, 2H). MS (DCI) m/e 494 $(M+H^+)$. Anal calcd for $C_{30}H_{39}NO_5$: C, 72.99; H, 7.96; N, 2.84. Found: C, 72.73; H, 7.89; N, 2.64.

Example 387

trans, trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-*n*-hexanesulfonylamino)ethyl]pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared and isolated as a white solid. m.p. 63-65 °C. ^1H NMR ($CDCl_3$, 300MHz) δ 0.82 (t, J=7Hz, 3H), 0.88 (t, J=6Hz, 3H), 1.23-1.47 (m, 6H), 1.44 (sextet, J=7Hz, 2H), 1.71 (quintet, J=6Hz, 2H), 2.24-2.34 (m, 1H), 2.70-2.93 (m, 5H), 2.96-3.12 (m, 2H), 3.15-3.35 (m, 2H), 3.43 (dd, J=3Hz, J=9Hz, 1H), 3.52-3.59 (m, 1H), 3.66 (d, J=9Hz, 1H), 3.87 (s, 3H), 5.95 (s, 2H), 6.74 (d, J=8Hz, 1H), 6.82 (d, J=8Hz, 1H), 6.42 (t, J=8Hz, 1H), 6.96 (s, 1H), 7.12 (d, J=9Hz, 1H), 7.17 (d, J=12Hz, 1H). MS (DCI/NH_3) m/e 593 $(M+H)^+$.

Example 388

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-((3-pyridyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 2.87 (m, 2H), 3.04 (dd, J=3.2, 9.7 Hz, 1H), 3.21 (d, J=13.7 Hz, 1H), 3.51 (m, 1H), 3.76-3.85 (m, 2H), 3.79 (s, 3H), 5.90 (m, 2H),

6.71 (m, 1H), 6.79 (dd, J=1.7 Hz, 7.8H), 6.94 (m, 3H), 7.36-7.45 (m, 3H), 7.81 (m, 1H), 8.39 (m, 1H), 8.46 (dd, J=1.4 Hz, 1H). Anal calcd for $C_{25}H_{24}N_2O_5 \cdot 0.70\ H_2O \cdot 0.05\ CH_3CO_2C_2H_5$: C, 67.34; H, 5.79; N, 6.23. Found: C, 67.31; H, 5.63; N, 5.90.

Example 389

trans,trans-2-(*n*-Hexyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.82-1.00 (m, 9H), 1.20-1.40 (m, 12H), 1.45-1.60 (m, 4H), 1.70-1.90 (br m, 2H), 3.10-3.46 (m, 6H), 3.65 (t, J=10.8 Hz, 1H), 3.76 (t, J=11.0 Hz, 1H), 3.92-4.06 (m, 2H), 4.14-4.34 (m, 2H), 5.94 (s, 2H), 6.73 (d, J=8.1 Hz, 1H), 6.79 (dd, J=8.1, 1.8 Hz, 1H), 6.87 (d, J=1.8 Hz, 1H). MS(DCI/NH_3) m/e 489 $(M+H)^+$. Anal calcd for $C_{28}H_{44}N_2O_5 \cdot 0.9$ TFA: C, 60.53; H, 7.65; N, 4.74. Found: C, 60.62; H, 7.69; N, 4.61.

Example 390

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(((N-(2-pentyl)-N-(4-fluoro-3-methylphenyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 0.92 (m, 3H), 0.97 (t, J=7.1 Hz, 3H), 1.13-1.40 (m, 4H), 2.22 (m, 3H), 2.58-2.74 (m, 1H), 2.78-2.87 (m, 1H), 3.09-3.25 (m, 2H), 3.39-3.60 (m, 2H), 3.70-3.90 (m, 1H), 3.80 (s, 3H), 4.70 (m, 1H), 5.93 (m, 2H), 6.70-6.76 (m, 1H), 6.75 (dd, J=1.4, 8.1 Hz, 1H), 6.80-6.94 (m, 4H), 6.96-7.13 (m, 4H). MS (DCI.) m/e 577 $(M+H^+)$. Anal calcd for $C_{33}H_{37}FN_2O_6 \cdot 0.25\ H_2O$: C, 68.20; H, 6.50; N, 4.82. Found: C, 68.21; H, 6.46; N, 4.74.

Example 391

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-((2-pyridyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 2.97 (dd, J=7.9, 9.7 Hz, 1H), 3.04 (t, J=9.6 Hz, 1H), 3.18 (dd, J=4.4 Hz, 9.9H), 3.47 (d, J=14.0 Hz, 1H), 3.59 (m, 1H), 3.78 (s, 3H), 3.96 (d, J=9.9 Hz, 1H), 3.97 (d, J=13.6 Hz, 1H), 5.90 (m, 2H), 6.73 (d, J=8.1 Hz, 1H), 6.83 (dd, J=1.7, 7.9 Hz, 1H), 6.92 (m, 2H), 6.96 (d, J=1.8 Hz, 1H), 7.28 (m, 1H),

7.44 (m, 2H), 7.53 (d, J=8.1 Hz, 1H), 7.80 (dt, J=1.8, 7.7 Hz, 1H), 8.42 (m, 1H). MS (DCI) m/e 433 ($M+H^+$). Anal calcd for $C_{25}H_{24}N_2O_5 \cdot 0.35\ H_2O$: C, 68.43; H, 5.67; N, 6.38. Found: C, 68.44; H, 5.61; N, 6.24.

Example 392

trans, trans-2-(3-Phenylpropyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89-0.97 (m, 6H), 1.22-1.36 (m, 4H), 1.41-1.55 (m, 4H), 1.63-1.95 (m, 4H), 2.62 (dt, J=7.2, 2.1 Hz, 2H), 3.05-3.44 (m, 7H), 3.53-3.60 (m, 2H), 3.65-3.76 (m, 1H), 3.82-3.90 (m, 1H), 3.96-4.10 (m, 1H), 5.92 (s, 2H), 6.71 (d, J=8.1 Hz, 1H), 6.77 (dd, J=8.1, 1.5 Hz, 1H), 6.86(d, J=1.2 Hz, 1H), 7.10-7.28 (m, 5H). MS(DCI/NH_3) m/e 523 $(M+H)^+$. Anal calcd for $C_{31}H_{42}N_2O_5 \cdot$ 0.6 TFA: C, 65.43; H, 7.26; N, 4.74. Found: C, 65.28; H, 7.29; N, 4.50.

Example 393

trans-trans-2-(4-Methoxy-3-fluorophenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared and isolated as a white solid. m.p. 115-117 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, J=7Hz, 3H), 0.88 (t, J=7Hz, 3H), 1.05-1.5 (m, 8H), 2.85 (d, J=13Hz, 1H), 2.90-3.17 (m, 5H), 3.20-3.35 (m, 1H), 3.35-3.50 (m, 3H), 3.55-3.65 (m, 1H), 3.84 (d, J=10Hz, 1H), 3.87 (s, 3H), 3.92 (s, 3H), 5.94 (dd, J=4Hz, 2Hz, 2H), 6.62 (s, 1H), 6.70 (s, 1H), 6.90 (t, J=8Hz, 1H), 7.05-7.20 (m, 2H).

Example 394

trans-trans-2-(1,4-Benzodioxan-6-yl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared and isolated as a white solid. m.p. 107-110 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, J=7Hz, 3H), 0.88 (t, J=7Hz, 3H), 1.05-1.50 (m, 8H), 2.75 (d, J=13Hz, 1H), 2.90-3.12 (m, 4H), 3.32-3.60 (m, 5H), 3.69 (d, J= 8Hz, 1H), 3.90 (s, 3H), 4.23 (s, 4H), 5.95 (dd, J=4Hz, 2Hz, 2H), 6.62 (s, 1H), 6.70 (s, 1H), 6.78-6.93 (m ,3H).

Example 395

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(3-butyl-2-fluoro-hept-2-en-1-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.84 (t, J=7.0 Hz, 3H), 0.88 (t, J=7.0 Hz, 3H), 1.16-1.37 (m, 8H), 1.83 (t, J=8.5 Hz, 2H), 2.03-2.08 (m, 2H), 2.76-2.92 (m, 2H), 3.02 (t, J=9.3 Hz, 1H), 3.32-3.42 (m, 2H), 3.50 (m, 1H), 3.71 (d, J=9.2 Hz, 1H), 3.78 (s, 3H), 5.91 (m, 2H), 6.72 (d, J=7.8 Hz, 1H), 6.83 (dd, J=1.7, 8.1 Hz, 1H), 6.90 (m, 2H), 7.02 (d, J=1.7 Hz, 1H), 7.34 (m, 2H). MS (DCI) m/e 512 (M+H$^+$). Anal calcd for $C_{30}H_{38}FNO_5$: C, 70.43; H, 7.49; N, 2.74. Found: C, 70.58; H, 7.54; N, 2.66.

Example 396

trans,trans-2-(3-Fluoro-4-ethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-*n*-pentanesulfonylamino)ethyl]pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared and isolated as a white solid. m.p. 65-66 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, J=7Hz, 3H), 0.90 (t, J=7Hz, 3H), 1.26-1.36 (m, 4H), 1.41-1.52 (m, 5H), 1.73 (quintet, J=7Hz, 2H), 2.23-2.33 (m, 1H), 2.69-2.96 (m, 5H), 2.97-3.12 (m, 2H), 3.16-3.37 (m, 2H), 3.43 (d, J=9Hz, 1H), 3.52-3.59 (m, 1H), 3.66 (d, J=9Hz, 1H), 4.08 (q, J=7Hz, 2H), 5.95 (s, 2H), 6.74 (d, J=8Hz, 1H), 6.82 (d, J=8Hz, 1H), 6.92 (t, J=8Hz, 1H), 6.97 (s, 1H), 7.07 (d, J=8Hz, 1H), 7.15 (d, J=12Hz, 1H). MS (DCI/NH_3) m/e 593 (M+H)$^+$.

Example 397

trans,trans-2-(4-Methoxy-3-fluorophenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[(N-butyl-N-propylamino)carbonylmethyl]pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared and isolated as a white solid. m.p. 118-120 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.70-0.90 (4 triplets, J=7Hz), 1.05-1.55 (m, 8H), 2.80-3.50 (m, 9H), 3.55-3.65 (m, 1H), 3.82 (d, J= 10Hz, 1H), 3.85 (s, 3H), 3.92 (s, 3H), 5.96 (s, 2H), 6.62 (s, 1H), 6.70 (s, 1H), 6.90 (t, J=8Hz, 1H), 7.08-7.22 (m, 2H).

Example 398

trans,trans-4-(1,3-benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(N-butyl-N-(4-chlorophenyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.87 (t, J=7 Hz, 3H), 1.20-1.50 (m, 4H),

2.66-4.00 (m, 9H), 3.81 (s, 3H), 5.95 (s, 2H), 6.77 (d, J=7 Hz, 1H), 6.85 (d, J=8 Hz, 3H), 7.05 (m, 5H), 7.33-7.42 (m, 2H). MS (C.I,) m/e 565 (M+H). Analysis calcd for $C_{31}H_{33}N_2O_6Cl \cdot 0.25\ H_3PO_4$: C, 63.16; H, 5.77; N, 4.75. Found: C, 63.14; H, 5.59; N, 4.53.

Example 399

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(4-methyl-1,2,3,4-tetrahydroquinolin-1-yl)carbonylmethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 1.27 (d, J=7 Hz, 1.5H), 1.28 (d, 7H, 1.5-diastereomer), 1.39-1.55 (m, 1H), 2.02-2.15 (m, 1H), 2.60-3.25 (m, 5H), 3.33-4.00 (m, 5H), 3.78 (s, 3H), 5.92 (d, J=3 Hz, 2H), 6.73 (dd, J=8 Hz, 1H), 6.75-6.90 (m, 3H), 6.91-7.35 (m, 7H). MS (DCI) m/e 529 $(M+H)^+$. Analysis calcd for $C_{31}H_{32}N_2O_6$: C, 70.44; H, 6.10; N, 5.30. Found: C, 70.16; H, 6.04; N, 5.04.

Example 400

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-(2-(piperidin-1-yl)ethanesulfonylamino)ethyl]pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared and isolated as a white solid. m.p. 95-96 °C. ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.82 (t, J=7Hz, 3H), 1.43-1.55 (m, 4H), 1.63-1.72 (m, 4H), 2.29-2.38 (m, 1H), 2.64-2.78 (m, 5H), 2.87 (t, J=8Hz, 1H), 2.95-3.04 (m, 5H), 3.20-3.30 (m, 1H), 3.32-3.43 (m, 4H), 3.54-3.63 (m, 1H), 3.78 (d, J=8Hz, 1H), 3.87 (s, 3H), 5.92 (s, 2H), 6.72 (d, J=8Hz, 1H), 6.78 (dd, J=2Hz, J=8Hz, 1H), 6.88 (t, J=8Hz, 1H), 6.94 (d, J=2Hz, 1H), 7.08-7.20 (m, 2H). MS (DCI/NH_3) m/e 620 $(M+H)^+$.

Example 401

trans,trans-2-(*n*-Heptyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.83-0.98 (s, 9H), 1.18-1.40 (m, 14H), 1.44-1.60 (m, 4H), 1.72-1.96 (br m, 2H), 3.12-3.45 (m, 6H), 3.65 (t, J = 10.5 Hz, 1H), 3.76 (t, J = 11.2 1H), 3.90-4.06 (m, 2H), 4.13-4.33 (m, 2H), 5.93 (s, 2H), 6.73 (d, J = 7.8 Hz, 1H), 6.79 (dd, J = 7.8, 1.7 Hz, 1H), 6.87 (d, J = 1.7 Hz, 1H). MS(DCI/NH_3) m/e

503 $(M+H)^+$. Anal calcd for $C_{29}H_{46}N_2O_5 \cdot 0.75$ TFA: C, 62.28; H, 8.01; N, 4.76. Found: C, 62.20; H, 7.99; N, 4.50.

Example 402

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(3-methyl-1,2,3,4-tetrahydroquinolin-1-yl)carbonylmethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 0.99 (d, 1.5H), 1.03 (d, J=6 Hz, 1.5H, second diastereomer), 2.60-4.00m (12), 3.78 (s, 1.5H), 3.79 (s, 1.5H, second diastereomer), 5.92 (s, 1H), 5.93 (s, 1H, diastereomer), 6.65-7.40 (m, 11H). MS (DCI) m/e 529 $(M+H)^+$. Analysis calcd for $C_{31}H_{32}N_2O_6 \cdot 0.8\ H_2O$: C, 68.57; H, 6.24; N, 5.16. Found: C, 70.44; H, 6.10; N, 5.30.

Example 403

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(N-butyl-N-(4-fluorophenyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 0.87 (t, J=7 Hz, 3H), 1.2-1.47 (m, 4H), 2.7 (d, J=12 Hz, 1H), 2.80 (t, J=9 Hz, 1H), 3.09 (t, J=9 Hz, 1H), 3.25 (d, J=15 Hz, 1H), 3.40-3.47 (m, 1H), 3.49-3.65 (m, 3H), 3.75 (d, J=12 Hz, 1H), 3.80 (s, 3H), 5.94 (s, 2H), 6.72-6.86 (m, 4H), 7.00-7.15 (m, 7H). MS (DCI) m/e 549 $(M+H)^+$. Analysis calcd for $C_{31}H_{33}N_2O_6F \cdot 0.4\ H_2O$: C, 66.99; H, 6.13; N, 5.04. Found: C, 66.99; H, 5.94; N, 4.99.

Example 404

trans,trans-1-(N-Butyl-N-(3-methylphenyl)aminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(5-benzofuranyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300MHz, $CDCl_3$) δ 7.66 (1H, bs), 7.60 (1H, d, *J*=3Hz), 7.45 (2H, s), 7.15 (4H, m), 6.75 (5H, m), 3.96 (1H, d, *J*=10Hz), 3.78 (3H, s), 3.74 (1H, m), 3.59 (3H, m), 3.21 (1H, t, *J*=9Hz), 3.19 (1H, d, *J*=16Hz), 2.92 (1H, t, *J*=9Hz), 2.70 (1H, d, *J*=16Hz), 2.29 (3H, s), 1.41 (2H, m), 1.24 (2H, m), 0.85 (3H, t, *J*=7Hz). MS (DCI, NH_3) m/e 541 $(M+H^+)$. Anal. calcd for $C_{33}H_{34}N_2O \cdot 1\ H_2O$: C, 71.21; H, 6.52; N 5.03. Found: C, 71.31; H, 6.30; N, 4.98.

Example 405

trans,trans-1-(N-Butyl-N-(3-methylphenyl)aminocarbonylmethyl)-2-(4-fluorophenyl)-4-(5-benzofuranyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (1H, bs), 7.60 (1H, d, *J*=3Hz), 7.45 (2H, m), 7.18 (3H, m), 7.12 (1H, d, *J*=7Hz), 6.93 (2H, m), 6.76 (1H, d, *J*=3Hz), 6.70 (2H, bd), 4.02 (1H, m), 3.77 (1H, m), 3.59 (3H, m), 3.29 (1H, m), 3.19 (1H, m), 2.94 (1H, m), 2.71 (1H, m), 2.30 (3H, s), 1.45 (2H, m), 1.26 (2H, sext, *J*=7Hz), 0.84 (3H, t, *J*=7Hz). MS (DCI, NH_3) m/e 529 ($M+H^+$). Anal. calcd for $C_{33}H_{34}N_2O_5 \cdot 0.2$ HOAc: C, 71.98; H, 6.30; N 5.18. Found : C, 71.68; H, 5.89; N, 5.25.

Example 406

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-((N,N-(di-(3-methylphenyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 2.27 (s, 6H), 2.81 (dd, J=8.1, 9.5 Hz, 1H), 2.98 (d, J=15.3 Hz, 1H), 3.20 (t, J=16.6 Hz, 1H), 3.47-3.60 (m, 3H), 3.80 (s, 3H), 3.85 (d, J=9.5 Hz, 1H), 5.91 (s, 2H), 6.73 (d, J=7.8 Hz, 1H), 6.85 (m, 3H), 6.95 (m, 4H), 7.05 (d, J=1.7 Hz, 1H), 7.06-7.24 (m, 6H). MS (DCI) m/e 579 ($M+H^+$). Anal calcd for $C_{35}H_{34}N_2O_6 \cdot 0.15\ H_2O \cdot 0.20\ CH_3CO_2C_2H_5$: C, 71.79; H, 6.04; N, 4.68. Found: C, 71.81; H, 5.79; N, 4.51.

Example 407

trans,trans-4-(1,2-Dihydrobenzofuran-5-yl)-2-(4-methoxyphenyl)-1-(((N-butyl-N-(3-methylphenyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H (300MHz, $CDCl_3$) δ 7.73 (2H, m), 7.40-7.10 (4H, m), 6.92 (2H, m), 6.72 (2H, d, J=9), 6.63 (1H, m), 5.40 (1H, m), 4.55 (2H, t, J=9), 4.30-4.10 (3H, m), 3.84 (3H, s), 3.82 (1H, m), 3.65 (1H, m), 3.39 (1H, m), 3.21 (2H, t, J=9), 3.10-2.90 (2H, m), 2.26 (3H, s), 1.55 (2H, m), 1.45 (2H, m), 0.92 (3H, t, J=9). MS (DCI/NH_3) m/e 543 ($M+H^+$). Anal calcd for $C_{33}H_{38}N_2O_5 \cdot 0.65\ H_2O$: C, 71.50; H, 7.15; N, 5.05 . Found: C, 71.47; H, 6.96; N, 4.83.

Example 408

trans, trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-{2-(N-propyl-N-[2-(N,N-dimethylamino)]ethanesulfonylamino)ethyl}pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared and isolated as a white solid. m.p. 81-82 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, J=7Hz, 3H), 1.43 (sextet, J=7Hz, 2H), 2.15-2.24 (m, 1H), 2.36 (s, 6H), 2.66-2.76 (m, 1H), 2.83-3.04 (m, 6H), 3.18-3.41 (m, 5H), 3.55-3.63 (m, 1H), 3.72 (d, J=8Hz, 1H), 3.85 (s, 3H), 5.90 (d, J=6Hz, 2H), 6.67 (d, J=8Hz, 1H), 6.78 (dd, J=2Hz, J=8Hz, 1H), 6.84 (t, J=8Hz, 1H), 7.94 (d, J=2Hz, 1H), 7.09 (d, J=8Hz, 1H), 7.20 (dd, J=2Hz, J=12Hz, 1H). MS (DCI/NH_3) m/e 580 $(M+H)^+$.

Example 409

trans,trans-1-(N,N-Dibutylaminocarbonylmethyl)-2-(4-fluorophenyl)-4-(5-benzofuranyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (1H, bs), 7.80 (2H, m), 7.61 (1H, d, *J*=3Hz), 7.55 (1H, bd, *J*=8Hz), 7.46 (1H, d, *J*=8Hz), 7.07 (2H, t, *J*=8Hz), 6.76 (1H, d, *J*=3Hz), 5.53 (1H, bd, *J*=11Hz), 4.18 (2H, m), 3.91 (3H, m), 3.55 (1H, d, *J*=16Hz), 3.30 (3H, m), 3.12 (1H, dd, *J*=10&9Hz), 2.95 (1H, m), 1.51 (2H, m), 1.31 (4H, m), 1.12 (2H, m), 0.92 (3H, m), 0.83 (3H, t, *J*=7Hz). MS m/e (DCI, NH_3) 595 $(M+H^+)$.

Example 410

trans,trans-4-(1,2-Dihydrobenzofuran-5-yl)-2-(4-ethylphenyl)-1-(((N-butyl-N-(3-methylphenyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (2H, m), 7.20-7.00 (7H, m), 6.70 (2H, d, J=9), 5.38 (1H, m), 4.55 (2H, t, J=9), 4.05 (1H, m), 3.64 (2H, m), 3.45 (1H, m), 3.21 (2H, t, J=9), 2.95 (1H, m), 2.75 (1H, m), 2.63 (2H, q, J=8), 2.38 (2H, m), 2.27 (3H, s), 1.43 (2H, m), 1.30 (2H, m), 1.22 (3H, t, J=9), 0.89 (3H, t, J=9). MS (DCI/NH_3) m/e 541 $(M+H^+)$. Anal calcd for $C_{34}H_{40}N_2O_4 \cdot 1.6$ AcOH: C, 70.17; H, 7.34; N, 4.40. Found: C, 70.11; H, 7.06; N, 4.80.

Example 411

trans,trans-4-(1,2-Dihydrobenzofuran-5-yl)-2-(4-fluorophenyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (2H, m), 7.28 (1H, bs), 7.18 (1H, dd, J=8, 3), 7.00 (2H, t, J=9), 6.72 (1H, d, J=9), 4.53 (2H, t, J=9), 3.92 (1H, m), 3.65 (1H, m), 3.42 (3H, m), 3.19 (2H, t, J=9), 3.15-2.90 (6H, m), 1.43 (3H, m), 1.25 (3H, m), 1.10 (2H, m), 0.90 (3H, t, J=8), 0.83 (3H, t, J=8). MS (DCI/NH_3) m/e 497 ($M+H^+$). Anal calcd for $C_{29}H_{37}FN_2O_4 \cdot 0.25\ H_2O$: C, 69.51; H, 7.54; N, 5.59. Found: C, 69.45; H, 7.60; N, 5.44.

Example 412

trans,trans-4-(1,2-Dihydrobenzofuran-5-yl)-2-(4-fluorophenyl)-1-(((N-butyl-N-(3-methylphenyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (1H, bs), 7.25-7.00 (5H, m), 6.91 (2H, m), 6.72 (3H, d, J=9), 4.54 (2H, t, J=9), 4.00 (1H, m), 3.60 (3H, m), 3.45 (1H, m), 3.19 (2H, t, J=9), 3.11 (2H, m), 2.84 (1H, m), 2.67 (1H, bd, J=18), 2.26 (3H,s), 1.42 (2H, m), 1.25 (2H, m), 0.88 (3H, t, J=8). MS (DCI/NH_3) m/e 531 ($M+H^+$). Anal calcd for $C_{32}H_{35}FN_2O_4 \cdot 0.25\ H_2O$: C, 71.82; H, 6.69; N, 5.23. Found: C, 71.66; H, 6.55; N, 5.03.

Example 413

trans,trans-4-(Indan-5-yl)-2-(4-methoxyphenyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (3H, m), 7.18 (2H, m), 6.85 (2H, d, J=9), 3.83 (1H, m), 3.79 (3H, s), 3.67 (1H, m), 3.50-3.20 (4H, m), 3.20-2.92 (4H, m), 2.87 (5H, m), 2.79 (1H, bd, J=15), 2.06 (2H, m), 1.43 (2H, m), 1.27 (4H, m), 1.08 (2H, m), 0.88 (3H, t, J=8), 0.82 (3H, t, J=8). MS (DCI/NH_3) m/e 507 ($M+H^+$). Anal calcd for $C_{31}H_{42}N_2O_4$: C, 73.49; H, 8.36; N, 5.53. Found: C, 73.18; H, 8.29; N, 5.17.

Example 414

trans,trans-2-(4-Methoxyphenyl)-4-(3,4-difluorophenyl)-1-[(N-butyl-N-(3-methylphenyl)amino)carbonylmethyl]pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300MHz, $CDCl_3$) δ 0.86 (t, J=7Hz, 3H), 1.10-1.35 (m, 2H),

1.35-1.52 (m, 2H), 2.29 (s, 3H), 2.63 (d, J=13Hz, 1H), 2.76 (t, J=7Hz, 1H), 3.06-3.20 (m, 2H), 3.42-3.53 (m, 1H), 3.50-3.64 (m, 3H), 3.80 (s, 3H), 3.86 (d, J=9Hz, 1H), 6.66-6.82 (m, 4H), 7.02-7.22 (m, 6H), 7.30-7.40 (m, 1H).

Example 415

trans,trans-1-(N-Butyl-N-(3-chlorophenyl)aminocarbonylmethyl)-2-(4-fluorophenyl)-4-(5-benzofuranyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (1H, d, *J*=2Hz), 7.61 (1H, d, *J*=3Hz), 7.47 (1H, d, *J*=8Hz), 7.41 (1H, dd, *J*=8&3Hz), 7.30 (1H, dt, *J*=8&2Hz), 7.21 (1H, d, *J*=8Hz), 7.19 (2H, m), 7.00 (1H, bs), 6.94 (2H, t, *J*=8Hz), 6.83 (1H, bd, *J*=8Hz), 6.74 (1H, dd, *J*=2&1Hz), 3.96 (1H, d, *J*=10Hz), 3.75 (1H, ddd, 6, 5&3Hz), 3.59 (3H, m), 3.23 (1H, t, *J*=10Hz), 3.18 (1H, d, *J*=16Hz), 2.92 (1H, dd, *J*=10&9Hz), 2.69 (1H, d, *J*=16Hz), 1.41 (2H, m), 1.23 (2H, m), 0.87 (3H, t, *J*=7Hz). MS (DCI, NH_3) 549, 551 ($M+H^+$). Anal. calcd for $C_{31}H_{30}ClFN_2O$: C, 67.82; H, 5.51; N, 5.10. Found: C, 67.43; H, 5.33; N, 4.78.

Example 416

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(((N-propyl-N-(4-phenoxybenzyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, $CDCl_3$) δ (rotamer) 7.40-7.20 (5H, m), 7.13 (2H, m), 6.98 (2H, m), 6.93-6.60 (7H, m), 5.93 (1H, d, J=2), 5.88 (5.85) (1H, d, J=2), 4.90 (4.50) (1H, d, J=15), 4.10 (4.25) (1H, d, J=15), 3.77 (3.73) (3H, s), 3.72 (1H, m), 3.60 (1H, m), 3.53-3.20 (3H, m), 3.15-2.75 (4H, m), 1.60-1.20 (2H, m), 0.83 (0.64) (3H, t, J=8). MS (DCI/NH_3) m/e 623 ($M+H^+$). Anal calcd for $C_{37}H_{38}N_2O_7 \cdot 0.25\ H_2O$: C, 70.85; H, 6.19; N, 4.47. Found: C, 70.68; H, 6.10; N, 4.42.

Example 417

trans,trans-4-(1,2-Dihydrobenzofuran-5-yl)-2-(4-ethylphenyl)-1-(((N-(2-pentyl)-N-(4-fluoro-3-methylphenyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (1H, bs), 7.20-7.00 (5H, m), 6.87 (1H, m), 6.73 (2H, d, J=9), 6.57 (1H, m), 4.81 (1H, m), 4.55 (2H, t, J=9), 3.92 (1H, bd, J=11), 3.60 (1H, m), 3.43 (1H, m), 3.18 (2H, t, J=9), 3.17 (1H, m), 3.06 (1H, dd,

J=15, 6), 2.88 (1H, dd, J=11, 9), 2.61 (2H, q, J=8), 2.59 (1H, m), 2.18 (3H, m), 1.40-1.10 (4H ,m), 1.22 (3H, t, J=9), 1.00-0.80 (6H, m). MS (DCI/NH_3) m/e 573 ($M+H^+$). Anal calcd for $C_{35}H_{41}FN_2O_4 \cdot 0.75\ H_2O$: C, 71.71; H, 7.31; N, 4.78. Found: C, 71.56; H, 7.33; N, 4.56.

Example 418

trans,trans-2-(4-Methoxphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-[2-pyrimidinyl]amino)ethyl]pyrrolidine-3-carboxylic acid

Ethyl 2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propylamino)propyl]pyrrolidine-3-carboxylate, prepared by the procedures of Example 61B (300 mg), 138 mg of 2-bromopyrimidine, and 150 mg of diisopropylethylamine were heated at 95 °C for 15 hours in 2 mL of acetonitrile. The resulting intermediate trans-trans ethyl ester was isolated by chromatography on silica gel eluting with 5-10% ETOAc in CH_2Cl_2 and hydrolyzed with NaOH in ethanol/water to give 95 mg of the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, J=7Hz, 3H), 1.50 (sextet, J=7Hz, 2H), 2.15-2.30 (m, 1H), 2.75-2.97 (m, 3H), 3.40-3.55 (m ,4H), 3.60-3.70 (m, 3H), 3.75 (s, 3H), 5.95 (s, 2H), 6.34 (t, J=4Hz, 1H), 6.65 (d, J=8Hz, 1H), 6.75-6.82 (m, 1H), 6.78 (d, J=9Hz, 2H), 6.96 (d, J=2Hz, 1H), 7.27 (d, J=9Hz, 2H), 8.20 (d, J=4Hz, 2H).

Example 419

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(3-butyl-2-chloro-hept-2-en-1-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.84 (t, J=6.8 Hz, 3H), 0.88 (t, J=6.7 Hz, 3H), 1.19-1.39 (m, 8H), 2.05-2.09 (m, 2H), 2.17-2.23 (m, 2H), 2.78 (dd, J=6.6, 9.2 Hz, 1H), 2.95 (t, J=9.2 Hz, 1H), 3.32-3.37 (m, 2H), 3.49 (m, 1H), 3.70 (d, J=9.2 Hz, 1H), 3.77 (s, 3H), 5.91 (m, 2H), 6.72 (d, J=8.1 Hz, 1H), 6.85 (dd, J=1.9, 8.1 Hz, 1H), 6.89 (m, 2H), 7.08 (d, J=1.5 Hz, 1H), 7.36 (m, 2H). MS (DCI) m/e 528 ($M+H^+$). Anal calcd for $C_{30}H_{38}ClNO_5 \cdot 0.25\ H_2O$: C, 67.66; H, 7.29; N, 2.63. Found: C, 67.62; H, 7.18; N, 2.40.

Example 420

trans,trans-4-(1,2-Dihydrobenzofuran-5-yl)-2-(4-methoxyphenyl)-1-(((N-(2-pentyl)-N-(4-fluoro-3-methylphenyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (1H, bs), 7.15 (3H, m), 6.90 (1H, m), 6.77 (2H, dd, J=9, 3), 6.71 (2H, d, J=9), 6.56 (1H, m), 4.80 (1H, m), 4.53 (2H, t, J=9), 3.92 (1H, m), 3.79 (3H, s), 3.60 (1H, m), 3.45 (1H, m), 3.19 (2H, t, J=9), 3.18 (1H, m), 3.03 (1H, dd, J=15, 6), 2.85 (1H, m), 2.55 (1H, m), 2.18 (3H, m), 1.40-1.05 (4H, m), 1.00-0.80 (6H, m). MS (DCI/NH_3) m/e 575 ($M+H^+$). Anal calcd for $C_{34}H_{39}FN_2O_5 \cdot 0.35\ H_2O$: C, 70.29; H, 6.89; N, 4.82. Found: C, 70.37; H, 6.92; N, 4.30.

Example 421

trans,trans-4-(1,2-Dihydrobenzofuran-5-yl)-2-(4-methoxyphenyl)-1-(((N-butyl-N-(3-chlorophenyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (1H, d, J=3), 7.25-7.05 (5H, m), 6.98 (1H, bs), 6.80 (2H, m), 6.72 (2H, d, J=9), 4.53 (2H, t, J=9), 3.85 (1H, d, J=10), 3.79 (3H, s), 3.58 (3H, m), 3.42 (1H, dd, J=10, 6), 3.18 (4H, m), 2.87 (1H, m), 2.66 (1H, m), 1.40 (2H, m), 1.25 (2H, m), 0.86 (3H, t, J=9). MS (DCI/NH_3) m/e 563 ($M+H^+$). Anal calcd for $C_{32}H_{35}ClN_2O_5 \cdot 0.25\ H_2O$: C, 67.72; H, 6.30; N, 4.94. Found: C, 67.72; H, 6.21; N, 4.55.

Example 422

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(5-ethylfuran-2-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (1H, bs), 7.11 (1H, d, J=3), 7.02 (1H, dd, J=9, 3), 6.82 (1H, d, J=9), 6.52 (1H, d, J=4), 6.08 (1H, d, J=4), 5.98 (2H, s), 5.80 (1H, d, J=6), 4.70 (1H, bd, J=15), 4.37 (2H, m), 3.70 (2H, m), 3.39 (2H, m), 3.20 (1H, m), 3.10-2.82 (2H, m), 2.76 (2H, q, J=8), 1.45 (2H, m), 1.32 (3H, t, J=9), 1.30-1.10 (6H, m), 0.87 (3H, t, J=9), 0.85 (3H, t, J=9). MS (DCI/NH_3) m/e 499 ($M+H^+$). Anal calcd for $C_{28}H_{38}N_2O_6$ · 1.75 HCl: C, 59.80; H, 7.12; N, 4.98. Found: C, 59.51; H, 6.96; N, 4.88.

Example 423

trans,trans-4-(1,2-Dihydrobenzofuran-5-yl)-2-(4-fluorophenyl)-1-(((N-(2-pentyl)-N-(4-fluoro-3-methylphenyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.10 (4H, m), 6.92 (3H, m), 6.73 (2H, d, J=9), 6.59 (1H, m), 4.80 (1H, m), 4.53 (2H, t, J=9), 4.00 (1H, bd, J=10), 3.62 (1H, m), 3.45 (1H, m), 3.22 (1H, m), 3.21 (2H, t, J=9), 3.02 (1H, dd, J=15, 6), 3.85 (1H, t, J=10), 2.58 (1H, bd, J=18), 2.20 (3H, bs), 1.40-1.30 (3H, m), 1.15 (1H, m), 1.00-0.80 (6H, m). MS (DCI/NH_3) m/e 563 ($M+H^+$). Anal calcd for $C_{33}H_{36}F_2N_2O_4$: C, 70.44; H, 6.45; N, 4.98. Found: C, 70.06; H, 6.47; N, 4.71.

Example 424

trans,trans-4-(1,2-Dihydrobenzofuran-5-yl)-2-(4-fluorophenyl)-1-(((N-butyl-N-(3-chlorophenyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (2H, m), 7.25-7.10 (4H, m), 6.95 (3H, m), 6.82 (1H, bd, J=9), 6.73 (1H, d, J=9), 4.55 (2H, t, J=9), 3.92 (1H, bd, J=11), 3.60 (3H, m), 3.43 (1H, dd, J=9, 6), 3.21 (2H, t, J=9), 3.16 (2H, m), 2.87 (1H, m), 2.69 (1H, m), 1.42 (2H, m), 1.26 (2H, m), 0.87 (3H, t, J=9). MS (DCI/NH_3) m/e 551 ($M+H^+$). Anal calcd for $C_{31}H_{32}ClFN_2O_4$ · 0.25 H_2O: C, 67.02; H, 5.90; N, 5.04. Found: C, 66.98; H, 5.71; N, 4.76.

Example 425

trans,trans-4-(1,2-Dihydrobenzofuran-5-yl)-2-(4-ethylphenyl)-1-(((N-butyl-N-(3-chlorophenyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (1H, m), 7.21 (1H, d, J=9), 7.15 (2H, m), 7.09 (4H, bs), 6.96 (1H, bs), 6.80 (1H, bd, J=9), 6.73 (1H, d, J=9), 4.54 (2H, t, J=9), 3.89 (1H, bd, J=11), 3.60 (3H, m), 3.43 (1H, m), 3.22 (2H, t, J=9), 3.18 (2H, m), 2.92 (1H, m), 2.72 (1H, m), 2.62 (2H, q, J=8), 1.41 (2H, m), 1.26 (2H, m), 1.23 (3H, t, J=9), 0.87 (3H, t, J=9). MS (DCI/NH_3) m/e 561 ($M+H^+$). Anal calcd for $C_{33}H_{37}ClN_2O_4 \cdot 0.25\ H_2O$: C, 70.08; H, 6.68; N, 4.95. Found: C, 70.13; H, 6.59; N, 4.65.

Example 426

trans,trans-1-(N-Butyl-N-(3-chlorophenyl)carboxamidomethyl)-2-(4-methoxyphenyl)-4-(5-benzofuranyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (1H, bs), 7.60 (1H, d, *J*=3Hz), 7.48 (1H, d, *J*=8Hz), 7.42 (1H, dd, *J*=8&3Hz), 7.29 (1H, dt, *J*=8&3Hz), 7.21 (1H, d, *J*=8Hz), 7.14 (2H, m), 6.99 (1H, bs), 6.76 (4H, m), 3.88 (1H, d, *J*=10Hz), 3.75 (1H, ddd, *J*=6, 5&3Hz), 3.59 (2H, m), 3.53 (1H, dd, *J*=10&3Hz), 3.22 (1H, t, *J*=9Hz), 3.19 (1H, m), 2.96(1H, m), 2.70 (1H, d, *J*=16Hz), 1.42 (2H, m), 1.26 (2H, m), 0.87 (3H, t, *J*=7Hz). MS (DCI, NH_3) m/e 563, 561 ($M+H^+$). Anal. calcd for $C_{32}H_{33}ClN_2O_5 \cdot 0.5\ H_2O$: C, 67.42; H, 6.01; N, 4.91. Found: C, 67.45; H, 5.82; N, 4.68.

Example 427

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(((N-cyclohexyl-N-butylamino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, $CDCl_3$) (rotamer) δ 0.78 (0.86) (t, 3H, J=7Hz), 0.90-1.90 (envelope, 14H), 2.69 (2.80) (d, 1H, J=12Hz), 2.9-3.8 (envelope, 10H), 3.78 (3.80) (s, 3H), 5.92 (s, 2H), 6.72 (d, 1H, J=9Hz) 6.86 (m, 3H) 7.03 (d, 1H, J=6Hz), 7.34 (m, 2H). MS (DCI/NH_3) m/e 537 $(M+H)^+$. Anal. calc'd for $C_{31}H_{40}N_2O_6 \cdot 1\ H_2O$: C, 67.13; H, 7.63; N, 5.05. Found: C, 67.09; H, 7.34; N, 4.92.

Example 428

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-ethylphenyl)-1-(((N-(3-methylphenyl)-N-butylamino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, 3H, J=7Hz), 1.22 (t, 3H, J=7Hz), 1.25 (m, 2H), 1.43 (m, 2H), 2.26 (s, 3H), 2.6 (q, 2H, J=7Hz), 2.68 (d, 1H, J=12Hz), 2.86 (t, 1H, J=8Hz), 3.19 (q, 2H, J=7Hz), 3.44 (dd, 1H, J= 3Hz,10Hz), 3.59 (m, 3H), 3.94 (d, 1H, 9Hz), 5.92 (s, 2H), 6.75 (m, 3H), 6.86 (dd, 1H, J= 2Hz, 8Hz), 7.08 (m, 6H), 7.17 (t, 1H, J= 8Hz). MS (DCI/NH_3) m/e 543 $(M+H)^+$. Anal. calc'd for $C_{33}H_{38}N_2O_5 \cdot 0.60\ H_2O$: C, 71.61; H, 7.14; N, 5.06. Found: C, 71.57; H, 6.80; N, 4.87.

Example 429

trans,trans-4-(Benzofuran-5-yl)-2-(4-ethylphenyl)-1-(((N-(3-methylphenyl)-N-butylamino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, J=7Hz), 1.30 (t, 3H, J=7Hz), 1.31 (m, 2H), 1.43 (m, 2H), 2.27 (s, 3H), 2.73 (q, 2H, J=7Hz), 3.15 (d, 2H, J=17Hz), 3.61 (t, 2H, J= 8Hz), 3.82 (m, 2H), 4.00 (t, 1 H, 12Hz), 4.26 (m, 2H), 5.53 (br d, 1H), 6.54 (br s, 2H), 6.76 (d, 1H, J= 2Hz), 7.14 (m, 3H), 7.28 (s, 1H), 7.40 (m, 3H), 7.48 (d, 1H, J= 8Hz), 7.63 (d, 1H, J=2Hz), 7.73 (s, 1H). HRMS. calc'd for $C_{34}H_{39}N_2O_4$ $(M+H)^+$: 539.2910. Found: 539.2891

Example 430

trans,trans-4-(1,4-Benzodioxan-6-yl)-2-(4-ethylphenyl)-1-(((N-(3-methylphenyl)-N-butylamino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3H, J=7Hz), 1.22 (t, 3H, J=7Hz), 1.24 (m, 2H), 1.42 (m, 2H), 2.30 (s, 3H), 2.61 (q, 2H, J=7Hz), 2.67 (d, 1H, J=14Hz), 2.86 (t, 1H, J= 8Hz), 3.18 (q, 2H, J=7Hz), 3.41 (dd, 1 H, J=4,10Hz), 3.59 (m, 3H), 3.93 (d, 1H, J=10Hz), 4.25 (m, 4H), 6.74 (br s, 2H), 6.80 (d, 1H, J=8Hz), 6.93 (dd, 1H, J=2Hz,8Hz), 6.99 (d, 1H, J=2Hz), 7.07 (m, 5H), 7.17 (t, 1H, J=8Hz). MS (DCI/NH_3) m/e 557 $(M+H)^+$. Anal. calc'd for $C_{34}H_{40}N_2O_5 \cdot 0.40\ H_2O$: C, 72.42; H, 7.29; N, 4.97. Found: C, 72.49; H, 7.16; N, 4.62.

Example 431

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-2-mesitylenesulfonylamino)ethyl]pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared and isolated as a white solid. m.p. 80-82 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.69 (t, J=7Hz, 3H), 1.37 (sextet, J=7Hz, 2H), 2.09-2.17 (m, 1H), 2.24 (s, 3H), 2.53 (s, 6H), 2.54-2.64 (m, 1H), 2.73-2.86 (m, 2H), 3.02 (sextet, J=7Hz, 2H), 3.13-3.28 (m, 3H)), 3.44-3.53 (m, 1H), 3.57 (d, J=9Hz, 1H), 3.89 (s, 3H), 5.94 (s, 2H), 6.74 (d, J=8Hz, 1H), 6.78 (dd, J=2Hz, J=8Hz, 1H), 6.85 (s, 2H), 6.92 (d, J=8Hz, 1H), 9.94 (d, J=2Hz, 1H), 7.06 (d, J=8Hz, 1H), 7.13 (dd, J=2Hz, J=12Hz, 1H). MS (DCI/NH_3) m/e 627 $(M+H)^+$.

Example 432

trans,trans-2-(4-Methoxyphenyl)-4-(3,4-difluorophenyl)-1-[(N-butyl-N-(3-chlorophenyl)amino)carbonylmethyl]pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J=7Hz, 3H), 1.18-1.32 (m, 2H), 1.35-1.48 (m, 2H), 2.64 (d, J=13Hz, 1H), 2.71 (t, J= 7Hz, 1H), 3.08-3.18 (m, 2H), 3.42-3.48 (m, 1H), 3.53-3.64 (m, 3H), 3.77 (s, 3H), 3.80 (d, J=9Hz, 1H), 6.73-6.85 (m, 3H), 6.94 (s, 1H), 7.04-7.40 (m, 7H).

Example 433

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-(3-chloropropanesulfonyl)amino)ethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.80 (t, 3H, J=7), 1.47 (bd hex, 2H, J=8), 2.15 (pen, 2H, J=7), 2.32 (m, 1H), 2.7-3.2 (m, 9H), 3.46 (dd, 1H, J=4, 10), 3.57 (m, 1H), 3.64 (t, 2H, J=6), 3.67 (d, 1H, J=9), 3.86 (s, 3H), 5.92 (s, 2H), 6.74 (d, 1H, J=8), 6.84 (dd, 1H, J=2, 8), 6.96 (d, 1H, J=2), 7.06 (t, 1H, J=9), 7.18 (m, 2H). MS (DCI/NH_3) m/e 585 (M+H; ^{35}Cl)$^+$; 587 (M+H; ^{37}Cl)$^+$. Anal calcd for $C_{27}H_{34}N_2O_7ClFS$: C, 55.43; H, 5.86; N, 4.79. Found: C, 55.65; H, 5.81; N, 4.70.

Example 434

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-isobutyl-N-(3-chloropropanesulfonyl)amino)ethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared. ^1H NMR (CD_3OD, 300 MHz) δ 0.79 (d, 3H, J=7), 0.84 (d, 3H, J=7), 1.68 (hept, 1H, J=7), 2.18 (pen, 2H, J=7), 2.8-3.4 (m, 10H), 3.5-3.8 (m, 3H), 3.65 (t, 2H, J=6), 3.90 (s, 3H), 5.94 (s, 2H), 6.77 (d, 1H, J=8), 6.87 (dd, 1H, J=2, 8), 6.99 (d, 1H, J=2), 7.13 (t, 1H, J=9), 7.27 (m, 2H). MS (DCI/NH_3) m/e 599 $(M+H)^+$. Anal calcd for $C_{28}H_{36}N_2O_7ClFS \cdot 0.3$ TFA: C, 54.24; H, 5.78; N, 4.42. Found: C, 54.19; H, 5.71; N, 4.01.

Example 435

trans,trans-2-Propoxymethyl-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87-0.98 (m, 9H), 1.21-1.39 (m, 4H), 1.43-1.57 (m, 4H), 1.58-1.70 (m, 2H), 3.13-3.29 (m, 4H), 3.34-3.43 (m, 3H), 3.45-3.55 (m, 3H), 3.69 (dd, J = 10.2, 4.5 Hz, 1H), 3.80-4.20 (m, 4H), 5.93 (s, 2H), 6.73 (d, J = 7.8 Hz, 1H), 6.84 (dd, J = 8.2, 1.7 Hz, 1H), 6.93 (d, J = 1.7 Hz, 1H). MS(DCI/NH_3) m/e 477 $(M+H)^+$. Anal calcd for $C_{26}H_{40}N_2O_6 \cdot 0.50$ TFA: C, 60.77; H, 7.65; N, 5.25. Found: C, 60.73; H, 7.74; N, 5.22.

Example 436

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-(4-methylbutanesulfonyl)amino)ethyl]pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared and isolated as a white solid. m.p. 65-67 °C. ^1H NMR ($CDCl_3$, 300MHz) δ 0.82 (t, J=7Hz, 3H), 0.88 (d, J=5Hz, 6H), 1.46 (sextet, J=7Hz, 2H), 1.56-1.64 (m, 3H), 2.24-2.33 (m, 1H), 2.68-2.93 (m, 5H), 2.98-3.12 (m, 2H), 3.15-3.35 (m, 2H), 3.43 (dd, J=3Hz, J=9Hz, 1H), 3.52-3.58 (, 1H), 3.65 (d, J=12Hz, 1H), 3.87 (s, 3H), 5.95 (s, 2H), 6.73 (d, J=8Hz, 1H), 6.82 (dd, J=2Hz, J=8Hz, 1H), 6.92 (t, J=8Hz, 1H), 6.97 (d, J=2Hz, 1H), 7.10 (d, J=9Hz, 1Hz) , 7.16 (dd, J=2Hz, J=12Hz, 1H). MS (DCI/NH_3) m/e 579 $(M+H)^+$.

Example 437

trans,trans-2-(4-Methoxy-3-fluorophenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-(*n*-pentanesulfonyl)amino)ethyl]pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared. ^{1}H NMR (300MHz, $CDCl_3$) δ 0.81 (t, J=7Hz, 3H), 0.90 (t, J=9Hz, 3H), 1.25-1.35 (m, 4H), 1.44 (sextet, J=7Hz, 2H), 1.67-1.78 (m, 2H), 2.22-2.34 (m, 1H), 2.30-2.95 (m, 5H), 2.95-3.10 (m, 2H), 3.15-3.33 (m, 2H), 3.45 (dd, J=3Hz, 9Hz, 1H), 3.47-3.56 (m, 1H), 3.65 (d, J=9Hz, 1H), 3.88 (s, 3H), 3.94 (s, 3H), 5.95 (s, 2H), 6.55 (s, 1H), 6.65 (s, 1H), 6.92 (t, J=7H, 1H), 7.11 (d, J=9Hz,1H), 7.17 (d, J=12Hz, 1H).

Example 438

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-(2,2,3,3,3-pentafluoropropoxyethanesulfonyl)amino)ethyl]pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared and isolated as a white solid. m.p. 63-64 °C. ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.82 (t, J=7Hz, 3H), 1.45 (sextet, J=7Hz, 2H), 2.24-2.33 (m, 1H), 2.70-2.82 (m, 1H), 2.85-3.09 (m, 5H), 3.14-3.28 (m, 4H), 3.43 (dd, J=3Hz, J=9Hz, 1H), 3.52-3.58 (m, 1H), 3.65 (d, J=9Hz, 1H), 3.87 (s, 3H), 3.92-3.98 (m, 3H), 5.94 (s, 2H), 6.74 (d, J=8Hz, 1H), 6.82 (dd, J=2Hz, J=8Hz, 1H), 6.92 (t, J=8Hz, 1H), 6.97 (d, J=2Hz, 1H), 7.10 (d, J=9Hz, 1H), 7.17 (dd, J=2Hz, J=12Hz, 1H). MS (DCI/NH_3) m/e 685 $(M+H)^+$.

Example 439

trans,trans-2-(1,4-Benzodioxan-6-yl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-(*n*-pentanesulfonyl)amino)ethyl]pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared. ^{1}H NMR ($CDCl_3$) δ 0.81 (t, J=7Hz, 3H), 0.90 (t, J=7Hz, 3H), 1.23-1.36 (m, 4H), 1.45 (sextet, J=7Hz, 2H), 1.65-1.78 (m, 2H), 2.20-2.30 (m, 1H), 2.30-2.95 (m, 5H), 2.95-3.10 (m, 2H), 3.15-3.35 (m, 2H), 3.42 (dd, J=3Hz, 9Hz, 1H), 3.46-3.56 (m, 1H), 3.59 (d, J=9Hz, 1H), 3.91 (s, 3H), 4.24 (s, 4H), 5.95 (s, 2H), 6.57 (s, 1H), 6.68 (s, 1H), 6.82 (d, J=8Hz, 1H), 6.88 (dd, J=2Hz, 8Hz, 1H), 6.95 (d, J=2Hz, 1H).

Example 440

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(((N-butyl-N-(4-methoxybenzyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, $CDCl_3$) δ (rotamer) 7.32 (1H, d, J=10), 7.22 (1H, m), 7.10 (1H, d, J=9), 7.03 (6.98) (1H, d, J=3), 6.90-6.80 (4H, m), 6.79 (2H, d, J=9),

6.77 (1H, t, J=8), 5.85 (2H, s), 4.92 (4.10) (1H, d, J=15), 4.42 (4.22) (1H, d, J=15), 3.81 (1H, m), 3.79 (3.78) (3H, s), 3.76 (3H, s), 3.62 (1H, m), 3.43 (2H, m), 3.30-2.70 (5H, m), 1.42 (1H, m), 1.23 (2H, m), 1.01 (1H, m), 0.83 (0.75) (3H, t, J=8). MS (DCI/NH_3) m/e 575 ($M+H^+$). Anal calcd for $C_{33}H_{38}N_2O_7 \cdot 0.5\ H_2O$: C, 67.91; H, 6.73; N, 4.80. Found: C, 67.78; H, 6.44; N, 4.55.

Example 441

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-isobutyl-N-(pentanesulfonylamino)ethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared. ^1H NMR (CD_3OD, 300 MHz) δ 0.76 (d, 3H, J=7), 0.84 (d, 3H, J=7), 0.92 (t, 3H, J=7), 1.36 (m, 4H),1.70 (m, 3H), 2.90 (m, 2H), 3.02 (m, 2H), 3.1-3.8 (m, 7H), 3.84 (d, 2H, J=8), 3.91 (s, 3H), 5.96 (s, 2H), 6.80 (d, 1H, J=8), 6.88 (dd, 1H, J=2, 8), 7.00 (d, 1H, J=2), 7.19 (t, 1H, J=9), 7.35 (m, 2H). MS (DCI/NH_3) m/e 593 $(M+H)^+$. Anal calcd for $C_{30}H_{41}N_2O_7F \cdot 0.5$ TFA: C, 57.31; H, 6.44; N, 4.31. Found: C, 57.08; H, 6.15; N, 3,95.

Example 442

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(N-butyl-N-(3-fluorophenylamino)carbonylmethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 0.87 (t, J=7 Hz, 3H), 1.10-1.30 (m, 4H), 2.70-2.90 (m, 2H), 3.13 (t, J=8 Hz, 1H), 3.40-3.90 (m, 6H), 3.79 (s, 3H), 5.93 (s, 2H), 6.75 (d, J=8 Hz, 1H), 6.80-7.20 (m, 9H), 7.40 (m, 1H). MS (DCI) m/e 549 $(M+H)^+$. Anal calcd for $C_{31}H_{33}N_2O_6F \cdot 0.8\ H_2O$: C, 66.13; H, 6.19; N, 4.98. Found: C, 66.21; H, 5.83; N, 4.84.

Example 443

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-fluorophenyl)-1-(N-butyl-N-(3-chlorophenylamino)carbonylmethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 0.87 (t, J=7 Hz, 3H), 1.20-1.50 (m, 4H), 2.65-2.85 (m, 2H), 3.05-3.85 (m, 7H), 5.93 (s, 2H), 6.75 (d, J=8 Hz, 1H), 6.85 (dd, J=8 Hz, 1H), 6.90-7.10 (m, 4H), 7.10-7.25 (m, 3H), 7.33-7.45 (m, 2H). MS (DCI) m/e

553 $(M+H)^+$. Anal calcd for $C_{30}H_{30}N_2O_5FCl$: C, 65.16; H, 5.47; N, 5.07. Found: C, 65.37; H, 5.41; N, 4.98.

Example 444

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(((N-butyl-N-(3,4-dimethoxybenzyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, $CDCl_3$) δ (rotamer) 7.33 (1H, d, J=10), 7.23 (1H, m), 7.03 (6.97) (1H, d, J=3), 6.90-6.60 (6H, m), 6.47 (1H, m), 5.93 (2H, m), 4.83 (4.09) (1H, d, J=15), 4.45 (4.22) (1H, d, J=15), 3.83 (3.86) (3H, s), 3.79 (1H, m), 3.77 (3.76) (3H, s), 3.75 (3.65) (3H, s), 3.60 (1H, m), 3.43 (2H, m), 3.28 (1H, m), 3.20-2.70 (4H, m), 1.43 (1H, m), 1.23 (2H, m), 1.02 (1H, m), 0.84 (0.77) (3H, t, J=8). MS (DCI/NH_3) m/e 605 $(M+H^+)$. Anal calcd for $C_{34}H_{40}N_2O_8$: C, 67.53; H, 6.67; N, 4.63. Found: C, 67.28; H, 6.63; N, 4.38.

Example 445

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(((N-butyl-N-(2-methoxybenzyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, $CDCl_3$) δ (rotamer) 7.33 (1H, d, J=10), 7.11 (2H, m), 7.03 (1H, dd, J=8, 3), 6.90-6.60 (7H, m), 5.93 (2H, m), 4.83 (4.15) (1H, d, J=15), 4.47 (4.30) (1H, d, J=15), 3.81 (1H, m), 3.78 (3.73) (3H, s), 3.72 (3H, s), 3.59 (1H, m), 3.43 (2H, m), 3.30 (1H, m), 3.20-2.70 (4H, m), 1.42 (1H, m), 1.23 (2H, m), 1.01 (1H, m), 0.83 (0.77) (3H, t, J=8). MS (DCI/NH_3) m/e 575 $(M+H^+)$. Anal calcd for $C_{33}H_{38}N_2O_7$: C, 68.97; H, 6.66; N, 4.87. Found: C, 68.70; H, 6.56; N, 4.61.

Example 446

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(((N-butyl-N-(3-methoxybenzyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, $CDCl_3$) δ (rotamer) 7.31 (1H, d, J=10), 7.13 (1H, d, J=9), 7.16 (1H, dt, J=8, 3), 7.03 (1H, dd, J=10, 2), 6.90-6.60 (6H, m), 6.50 (1H, m), 5.94 (2H, m), 4.82 (4.19) (1H, d, J=15), 4.50 (4.23) (1H, d, J=15), 3.78 (3.76) (3H, s), 3.77 (1H, m), 3.75 (3.67) (3H, s), 3.59 (1H, m), 3.57-3.35 (2H, m), 3.25 (1H, m), 3.20-2.70 (4H, m), 1.43 (1H, m), 1.23 (2H, m), 1.02 (1H, m), 0.84 (0.77) (3H, t, J=8).

MS (DCI/NH_3) m/e 575 ($M+H^+$). Anal calcd for $C_{33}H_{38}N_2O_7$: C, 68.97; H, 6.66; N, 4.87. Found: C, 68.72; H, 6.55; N, 4.60.

Example 447

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-(2-methoxyethyl)-N-(3-chloropropanesulfonyl)amino)ethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared. ^1H NMR (CD_3OD, 300 MHz) δ 2.15 (pen, 2H, J=7), 2.33 (m, 1H), 2.81 (m, 2H); 2.93 (t, 1H, J=9); 3.1-3.6 (m, 10H), 3.24 (s, 3H); 3.65 (t, 2H, J=6), 3.70 (d, 1H, J=9), 3.87 (s, 3H), 5.92 (s, 2H), 6.74 (d, 1H, J=8), 6.84 (dd, 1H, J=2, 8), 6.97 (d, 1H, J=2), 7.07 (t, 1H, J=9), 7.17 (m, 2H). MS (DCI/NH_3) m/e 601 $(M+H)^+$. Anal calcd for $C_{27}H_{34}N_2O_8ClFS$: C, 53.95; H, 5.70; N, 4.66. Found: C, 53.65; H, 5.49; N, 4.26.

Example 448

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-(2-methoxyethyl)-N-(pentanesulfonyl)amino)ethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared. ^1H NMR (CD_3OD, 300 MHz) δ 0.93 (m, 3H), 1.34 (m, 4H), 1.69 (m, 2H), 2.33 (m, 1H), 2.75-3.1 (m, 7H), 3.23 (s, 3H), 3.3-3.6 (m, 6H), 3.70 (d, 1H, J=9), 3.86 (s, 3H), 5.92 (s, 2H), 6.74 (d, 1H, J=8), 6.84 (dd, 1H, J=2, 8), 6.97 (d, 1H, J=2), 7.07 (t, 1H, J=9), 7.18 (m, 2H). MS (DCI/NH_3) m/e 595 $(M+H)^+$. Anal calcd for $C_{29}H_{39}N_2O_8FS$: C, 58.57; H, 6.61; N, 4.71. Found: C, 58.21; H, 6.29; N, 4.29.

Example 449

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(((N-4-heptyl)-N-(4-fluoro-3-methylphenylamino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 0.89 (m, 6H), 1.18-1.36 (m, 8H), 2.15 (bs, 1.5 (CH_3 rotamer)), 2.28 (bs, 1.5 (CH_3 rotamer)), 2.64 (t, J=14.9 Hz, 1H), 2.82 (m, 1H), 3.07-3.29 (m, 2H), 3.32-3.41 (m, 1H), 3.53-3.60 (m, 1H), 3.70-3.79 (m, 1H), 3.79 (s, 3H), 4.68 (m, 1H), 5.92 (m, 2H), 6.69-6.90 (m, 6H), 6.93-7.07 (m, 4H). MS (DCI) m/e 605 ($M+H^+$). Anal calcd for $C_{35}H_{41}FN_2O_6$: C, 69.52; H, 6.83; N, 4.63. Found: C, 69.31; H, 6.78; N, 4.35.

Example 450

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(((N-(5-nonyl)-N-(4-fluoro-3-methylphenyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.81-0.90 (m, 6H), 1.30 (m, 12H), 2.14 (s, 1.5 (CH_3 rotamer)), 2.30 (s, 1.5 (CH_3 rotamer)), 2.60 (t, J=14.8 Hz, 1H), 2.80 (m, 1H), 3.09-3.24 (m, 2H), 3.33-3.42 (m, 1H), 3.50-3.55 (m, 1H), 3.65-3.77 (m, 1H), 3.79 (s, 3H), 4.64 (m, 1H), 5.93 (m, 2H), 6.70-6.84 (m, 5H), 6.91-7.13 (m, 5H). MS (DCI) m/e 633 ($M+H^+$). Anal calcd for $C_{37}H_{45}FN_2O_6$: C, 70.23; H, 7.17; N, 4.43. Found: C, 70.14; H, 7.13; N, 4.19.

Example 451

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-((N-(5-nonylamino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.80 (t, J=7.0 Hz, 3H), 0.84 (t, J=7.1 Hz, 3H), 1.15-1.55 (m, 12H), 2.88 (d, J=15.9 Hz, 1H), 3.07 (m, 2H), 3.26 (d, J=16.3 Hz, 1H), 3.36 (dd, J=4.4, 9.8 Hz, 1H), 3.64 (m, 1H), 3.76 (m, 1H), 3.79 (s, 3H), 3.98 (d, J=9.5 Hz, 1H), 5.93 (m, 2H), 6.77 (d, J=7.8 Hz, 1H), 6.85 (dd, J=1.7, 8.1 Hz, 1H), 6.93 (m, 2H), 6.99 (d, J=1.7 Hz, 1H), 7.39 (m, 2H). MS (DCI) m/e 525 ($M+H^+$). Anal calcd for $C_{30}H_{46}N_2O_6 \cdot 0.35\ H_2O$: C, 67.86; H, 7.73; N, 5.28. Found: C, 67.87; H, 7.63; N, 5.11.

Example 452

trans, trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-((N-butyl-N-(2-fluorophenyl)amino)carbonylmethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.87 (dt, J=7 Hz, 3H), 1.15-1.32 (m, 4H), 3.77 (d, J=2 Hz, 3H), 2.65-5.92 (m, 9H), 5.93 (d, J=4 Hz, 2H), 6.70-6.90 (m, 4H), 7.00-7.45 (m, 7H). MS (DCI) m/e 549 $(M+H)^+$. Anal calcd for $C_{31}H_{33}N_2O_6 \cdot 0.4\ H_2O$: C, 66.99; H, 6.13; N, 5.04. Found: C, 67.01; H, 6.23; N, 4.68.

Example 453

trans,trans-2-(4-Methoxphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-(2-benzothiazolyl)amino)ethyl]pyrrolidine-3-carboxylic acid

The title compound was prepared by the method of Example 418, substituting 2-chlorobenzothiazole for 2-bromopyrimidine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J=7Hz, 3H), 1.59 (sextet, J=7Hz, 2H), 2.25-2.37 (m, 1H), 2.85-2.97 (m, 3H), 3.28-3.36 (m, 2H), 3.50-3.58 (m, 3H), 3.60-3.65 (m, 1H), 3.67 (d, J=9Hz, 1H),3.71 (s, 3H), 5.87 (d, J=2Hz, 1H), 5.91 (d, J=2Hz, 1H), 6.57 (d, J=8Hz, 1H), 6.73 (dd, J=2Hz, 9Hz, 1H), 6.76 (d, J=8 Hz, 2H), 6.91 (d, J=2Hz, 1H), 7.01 (t, J=8Hz, 1H), 7.22 (t, J=8Hz, 1H), 7.29 (d, J=8Hz, 2H), 7.40 (d, J=7Hz, 1H), 7.55 (d, J=7Hz, 1H).

Example 454

trans,trans-2-(2-Ethoxyethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, J = 7.4 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H), 1.19 (t, J = 7.0 Hz, 3H), 1.24-1.38 (m, 5H), 1.46-1.60 (m, 4H), 2.03-2.12 (m, 2H), 3.07 (t, J = 8.0 Hz, 1H), 3.07-3.34 (m, 6H), 3.43-3.52 (m, 3H), 3.59-3.74 (m, 3H), 3.80-4.01 (m, 2H), 5.93 (s, 2H), 6.72 (d, J = 8.1 Hz, 1H), 6.79 (dd, J = 8.2 Hz, 1.7 Hz, 1H), 6.87 (d, J = 1.7 Hz, 1H). MS(DCI/NH_3) m/e 477 $(M+H)^+$. Anal calcd for $C_{26}H_{40}N_2O_6 \cdot 0.4$ TFA: C, 61.64; H, 7.80; N, 5.36. Found: C, 61.63; H, 7.84; N, 5.29.

Example 455

trans,trans-2-(4-Methoxy-3-fluorophenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-(2-(morpholin-4-ylethyl)sulfonylamino)ethyl]pyrrolidine-3-carboxylic acid

Ethyl 2-(4-methoxy-3-fluorophenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-[2-vinylsulfonyl]amino)ethyl]pyrrolidine-3-carboxylic acid, prepared by the procedures of Example 125, was reacted with excess morpholine for 4 hours at room temperature. Chromatography on silica gel eluting with EtOAc gave a 65% yield of an intermediate ethyl ester which was hydrolyzed to the title compound with NaOH in ethanol/water. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, J=7Hz, 3H), 1.46 (sextet, J=7Hz, 2H), 2.43-2.52 (m, 4H), 2.70-2.92 (m, 5H), 2.97-3.33 (m, 6H), 3.60 (dd, J=3Hz, 9Hz, 1H), 3.51-3.59 (m, 1H), 3.62-3.70 (m, 5H), 3.88 (s, 3H), 5.95 (s, 2H), 6.72 (d, J=8Hz, 1H), 6.70 (dd, J=2Hz, 8Hz, 1H), 6.90 (t, J=9Hz, 1H), 6.96 (d, J=2Hz, 1H), 7.10 (d, J=8Hz, 1H), 7.18 (dd, J=2Hz, 12Hz, 1H).

Example 456

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-((2,2,2-trifluoroethoxyethane)sulfonyl)amino)ethyl]pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared and isolated as a white solid. m.p. 95-96 °C. ^{1}H NMR (CD_3OD, 300MHz) δ 0.80 (t, J=7Hz, 3H), 1.35-1.48 (m, 2H),3.07 (sextet, J=7Hz, 2H), 3.23-3.55 (m, 8H), 3.80-3.87 (m, 2H), 3.93 (s, 3H), 3.94-4.02 (m, 4H), 4.66 (d, J=12Hz, 1H), 5.96 (s, 2H), 6.83 (d, J=8Hz, 1H), 6.94 (d, J=8Hz, 1H),7.06 (d, J=2Hz, 1H), 7.23 (t, J=9Hz, 1H), 7.43 (d, J=9Hz, 1H), 7.49 (dd, J=2Hz,J=12Hz, 1H). MS (DCI/NH_3) m/e 635 $(M+H)^+$.

Example 457

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-fluorophenyl)-1-(N-butyl-N-(3-methylphenyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.87 (t, J=7 Hz, 3H), 1.20-1.50 (m, 4H), 2.31 (s, 3H), 2.65-2.80 (m, 2H), 3.19 (t, J=7 Hz, 1H), 3.25 (d, J=10 Hz, 1H), 3.35-3.65 (m, 4H), 3.79 (d, J=10 Hz, 1H), 5.93 (s, 2H), 6.74 (d, J=7 Hz, 1H), 6.80-6.90 (m, 3H), 6.91-7.09 (m, 3H), 7.10-7.35 (m, 4H). MS (DCI) m/e 533 $(M+H)^+$. Anal calcd for $C_{31}H_{33}N_2O_5F$: C, 69.91; H, 6.25; N, 5.26. Found: C, 69.56; H, 6.26; N, 5.23.

Example 458

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-(2-methoxyethyl)-N-(butanesulfonylamino)ethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.94 (m, 3H), 1.23 (hex, 2H, J=8), 1.69 (m, 2H), 3.08 (m,2H), 3.20 (s, 3H), 3.3-3.5 (m, 10H), 3.77 (m, 2H), 3.92 (s, 3H), 4.60 (m, 1H), 5.96 (s, 2H), 6.81 (d, 1H, J=8), 6.88 (dd, 1H, J=2, 8), 6.99 (d, 1H, J=2), 7.22 (t, 1H, J=9), 7.38 (m, 2H). MS (APCI) m/e 581 $(M+H)^+$. Anal calcd for $C_{28}H_{37}N_2O_8FS \cdot 1.1$ TFA: C, 51.37; H, 5.44; N, 3.97. Found: C, 51.27; H, 5.35; N, 4.11.

Example 459

trans, trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-(2-methylpropanesulfonyl)amino)ethyl]pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared and isolated as a white solid. m.p. 77-78 °C. ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.83 (t, J=7Hz, 3H),1.06 (d, J=6Hz, 6H),1.45 (q, J=7Hz, 2H), 2.20 (septet, J=6Hz, 1H), 2.26-2.36 (m, 1H), 2.62-2.78 (m, 3H), 2.85-2.95 (m, 2H), 2.97-3.10 (m, 2H), 3.15-3.35 (m, 2H), 3.43 (dd, J=3Hz, J=9Hz, 1H), 3.53-3.62 (m, 1H), 3.66 (d, J=9Hz, 1H), 3.88 (s, 3H), 5.95 (s, 2H), 6.74 (d, J=8Hz, 1H), 6.82 (dd, J=2Hz, J=8Hz, 1H), 6.92 (t, J=8Hz, 1H), 6.97 (d, J=2Hz, 1H), 7.12 (d, J=9Hz, 1H), 7.18 (dd, J=2Hz, J=12Hz, 1H). MS (DCI/NH_3) m/e 565 $(M+H)^+$.

Example 460

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(((N-butyl-N-(4-nitrobenzyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, $CDCl_3$) δ (rotamer) 8.11 (2H, m),7.32 (3H, dd, J=9, 2), 7.16 (7.07) (1H, bd, J=10), 6.98 (6.94) (1H, d, J=2), 6.85 (2H, d, J=9), 6.83-6.70 (2H, m), 5.99 (5.97) (2H, d, J=2), 5.02 (4.18) (1H, d, J=15), 4.63 (4.38) (1H, d, J=15), 3.79 (3.77) (3H, s), 3.72 (1H, d, J=10), 3.61 (1H, m), 3.48 (1H, bd, J=15), 3.43-3.20 (2H, m), 3.06 (2H, m), 2.90 (1H, m), 3.79 (1H, bd, J=14), 1.43 (1H, m), 1.23 (2H, m), 1.02 (1H, m), 0.84 (0.78) (3H, t, J=8). MS (DCI/NH_3) m/e 590 $(M+H^+)$. Anal calcd for $C_{32}H_{35}N_3O_8$: C, 65.18; H, 5.98; N, 7.13. Found: C, 65.89; H, 5.85; N, 6.85.

Example 461

trans,trans-2-(4-Ethylphenyl)-4-(3,4-difluorophenyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.78 (t, 3H, J=7), 0.87 (t, 3H, J=7), 1.02 (hex, 2H, J=7), 1.22 (t, 3H, J=7), 1.27 (m, 2H), 1.45 (m, 2H, J=7), 2.63 (q, 2H, J=7), 2.77 (d, 1H, J=14), 2.94 (dd, 1H, J=7, 9), 3.05 (m, 3H), 3.3-3.5 m, 3H), 3.44 (d, 1H, J=14), 3.66 (m, 1H), 3.75 (d, 1H, J=10), 7.20 (td, 2H, J=1,8), 7.22 (m, 2H), 7.32 (td, 2H, J=1,8), 7.43 (ddd, 1H, J=2,8,12). MS (DCI/NH_3) m/e 501 $(M+H)^+$. Anal calcd for $C_{29}H_{38}N_2O_3F_2 \cdot 0.6\ H_2O$: C, 68.11; H, 7.73; N, 5.48. Found: C, 68.03; H, 7.53; N, 5.37.

Example 462

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(N-butyl-N-(4-fluoro-3-methylphenyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.87 (t, J=7 Hz, 3H), 1.20-1.50 (m, 4H), 2.21 (d, J=2 Hz, 3H), 2.64 (d, J=14 Hz, 1H), 2.75 (dd, J=10 Hz, 1H), 3.05 (t, J=7 Hz, 1H), 3.25 (d, J=15 Hz, 1H), 3.35-3.70 (m, 5H), 3.77 (s, 3H), 5.92 (s, 2H), 6.70-6.92 (m, 6H), 6.96-7.10 (m, 4H). MS (DCI) m/e 563 $(M+H)^+$. Anal calcd for $C_{32}H_{35}N_2O_6F \cdot 0.5\ H_2O$: C, 67.24; H, 6.35; N, 4.90. Found: C, 67.16; H, 6.06; N, 4.81.

Example 463

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(N-butyl-N-((3-isopropyl)phenyl)amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.87 (t, 3H), 1.17 (d, J=7 Hz, 6H), 1.20-1.50 (m, 4H), 2.63 (d, J=15 Hz, 1H), 2.75 (t, J=7 Hz, 1H), 2.85 (m, 1H), 3.00 (t, J=7 Hz, 1H), 3.25 (d, J=15 Hz, 1H), 3.40-3.70 (m, 5H), 3.75 (s, 3H), 5.90 (s, 2H), 6.65-6.80 (m, 3H), 6.71 (dt, J=7 Hz, 3H), 7.07 (m, 3H), 7.20-7.35 (m, 2H). MS (DCI) m/e 573 $(M+H)^+$. Anal calcd for $C_{34}H_{40}N_2O_6 \cdot 0.15\ H_3PO_4$: C, 69.52; H, 6.94; N, 4.77. Found: C, 63.31; H, 6.72; N, 4.43.

Example 464

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(N-butyl-N-(3-ethylphenyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.87 (m, J=7 Hz, 3H), 1.16 (t, J=7 Hz, 3H), 1.20-1.47 (m, 4H), 2.50 (q, J=7 Hz, 2H), 2.70-2.85 (m, 2H), 3.13 (t, J=7 Hz, 1H), 3.20-4.5 (m, 6H), 3.78 (s, 3H), 3.83 (d, J=8 Hz, 1H), 5.92 (s, 2H), 6.72 (d, J=8 Hz, 1H), 6.80-6.90 (m, 5H), 7.02-7.13 (m, 3H), 7.15-7.25 (m, 2H). MS (DCI) m/e 559 $(M+H)^+$. Anal calcd for $C_{33}H_{38}N_2O_6 \cdot 0.3\ H_2O$: C, 70.27; H, 6.90; N, 4.97. Found: C, 70.31; H, 6.63; N, 4.60.

Example 465

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-ethylphenyl)-1-(((N-(3-chlorophenyl)-N-butylamino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3H, J=7Hz), 1.23 (t, 3H, J=7Hz), 1.28 (m, 2H), 1.41 (m, 2H), 2.63 (q, 2H, J=7Hz), 2.67 (m, 1H), 2.92 (m, 1H), 3.20 (m, 2H), 3.42 (m, 1 H), 3.60 (q, 2H, J=7Hz), 3.93 (m, 1H), 5.92 (s, 2H), 6.75 (d, 1H, J=8Hz), 6.84 (m, 3H), 6.95 (br s, 1H), 7.02 (s, 1H), 7.10 (br s, 3H), 7.25 (m, 2H). MS (APCI) m/e 563 $(M+H)^+$. Anal. calc'd for $C_{32}H_{35}N_2O_5Cl \cdot 0.80\ H_3PO_4$: C, 59.92; H, 5.88; N, 4.37. Found: C, 59.90; H, 5.83; N, 4.07.

Example 466

trans,trans-4-(1,4-Benzodioxan-6-yl)-2-(4-ethylphenyl)-1-(((N-(3-chlorophenyl)-N-butylamino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, 3H, J=7Hz), 1.23 (t, 3H, J=7Hz), 1.25 (m, 2H), 1.40 (m, 2H), 2.64 (q, 2H, J=7Hz), 2.70 (m, 1H), 2.95 (m, 1H), 3.20 (m, 2H), 3.40 (m, 1 H), 3.57 (m, 3H), 3.90 (m, 1H), 4.25 (s, 4H), 6.80 (d, 1H, J=8Hz), 6.95 (d, 1H, J=2Hz), 6.95 (m, 2H), 7.07 (br s, 3H), 7.22 (m, 3H). MS (APCI) m/e 577. $(M+H)^+$. Anal. calc'd for $C_{33}H_{37}N_2O_5Cl \cdot 0.85\ H_2O$: C, 66.90; H, 6.58; N, 4.73. Found: C, 66.92; H, 6.25; N, 4.36.

Example 467

trans,trans-4-(Benzofuran-5-yl)-2-(4-ethylphenyl)-1-(((N-(3-chlorophenyl)-N-butylamino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, 3H, J=7Hz), 1.26 (t, 3H, J=7Hz), 1.30 (m, 2H), 1.40 (m, 2H), 2.60 (q, 2H, J=7Hz), 2.72 (m, 1H), 2.93 (m, 1H), 3.22 (m, 2H), 3.50 (m, 1H), 3.55 (m, 2H), 3.75 (m, 1H), 3.90 (br d, 1H), 6.75 (d, 1H, J=1Hz), 6.80 (br d, 1H), 6.95 (br s, 1H), 7.08 (m, 4H), 7.20 (t, 1H, J=8Hz), 7.28 (t, 1H, J=8Hz), 7.42 (m, 2H), 7.58 (d, 1H, J=1Hz), 7.63 (s, 1H). MS (APCI) m/e 559 $(M+H)^+$. Anal. calc'd for $C_{33}H_{35}N_2O_4Cl \cdot 0.45\ H_2O$: C, 69.88; H, 6.38; N, 4.94. Found: C, 69.83; H, 6.04; N, 4.87.

Example 468

trans,trans-2-(4-Methoxy-3-fluorophenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[2-(N-butyl-N-phenylamino)ethyl]pyrrolidine-3-carboxylic acid

Ethyl 2-(4-methoxy-3-fluorophenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[2-(bromoethyl]-pyrrolidine-3-carboxylate, prepared using the procedures of Example 61A (300 mg), was reacted with N-butyl aniline (190 mg) in 1 mL of dioxane containing 130 mg of diisopropylethylamine to give the ethyl ester. The ester was hydroyzed with sodium hydroxide to give 148 mg of the title compound as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J=9Hz, 3H), 1.28 (sextet, J=7Hz, 2H), 1.46 (quintet, J=7Hz, 2H), 2.20-2.32 (m, 1H), 2.68-2.77 (m, 1H), 2.82-2.95 (m, 2H), 3.12-3.22 (m, 2H), 3.30-3.44 (m, 3H), 3.45-3.55 (m, 1H), 3.62 (d, J=9Hz, 1H), 3.83 (s, 3H), 3.90 (s, 3H), 5.95 (s, 2H), 6.51 (d, J=7Hz, 2H), 6.55-6.62 (m, 2H), 6.69 (d, J=2Hz, 1H), 6.84 (t, J=8Hz, 1H), 7.02-7.15 (m, 3H), 7.19 (dd, J=2Hz, 12Hz, 1H).

Example 469

trans,trans-4-(1,4-Benzodioxan-6-yl)-2-(4-ethylphenyl)-1-(((N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (t, 3H, J=7Hz), 0.88 (t, 3H, J=7Hz), 1.05 (q, 2H, J=7Hz), 1.23 (t, 3H, J=7Hz), 1.28 (m, 2H), 1.45 (m, 2H), 2.64 (q, 2H, J=7Hz), 2.78 (m, 1H), 2.9-3.2 (envelope, 4H), 3.30 (m, 1H), 3.40 (m, 3H), 3.60 (m, 1H), 3.80 (m, 1H), 4.25 (s, 4H), 6.80 (d, 1H, J=8Hz), 6.90 (m, 1H), 6.98 (d, 1H, J=2Hz), 7.17 (d, 2H, J=8Hz), 7.30 (m, 2H). MS (APCI) m/e 523 $(M+H)^+$. Anal. calc'd for $C_{31}H_{42}N_2O_5 \cdot 1.1$ HOAc: C, 67.73; H, 7.94; N, 4.76. Found: C, 67.81; H, 7.55; N, 4.48.

Example 470

trans,trans-4-(1,4-Benzodioxan-6-yl)-2-(4-methoxyphenyl)-1-((N-butyl-N-(3-methylphenylamino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.87 (t, J=7.1 Hz, 3H), 1.30 (m, 2H), 1.44 (m, 2H), 2.30 (s, 3H), 2.80 (d, J=15.2 Hz, 1H), 2.85 (t, J=9.3 Hz, 1H), 3.19 (t, J=9.3 Hz, 1H), 3.33 (d, J=10.2 Hz, 1H), 3.42-3.61 (m, 3H), 3.79 (s, 3H), 3.91 (d, J=9.8 Hz, 1H), 4.22 (m, 4H), 6.75-6.86 (m, 6H), 6.95 (d, J=2.0 Hz, 1H), 7.09 (d, J=8.8 Hz, 2H), 7.22 (d, J=10.2 Hz, 1H), 7.26 (t, J=7.6 Hz, 1H). MS (DCI) m/e 559 $(M+H^+)$. Anal calcd for $C_{33}H_{38}N_2O_6 \cdot 0.4\ CH_3CO_2C_2H_5$: C, 69.97; H, 6.99; N, 4.72. Found: C, 0.06; H, 6.66; N, 4.48.

Example 471

trans,trans-4-(1,4-Benzodioxan-6-yl)-2-(4-methoxyphenyl)-1-((N-butyl-N-(3-chlorophenylamino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 0.87 (t, J=7.0 Hz, 3H), 1.25 (m, 2H), 1.40 (m, 2H), 2.78 (d, J=14.6 Hz, 1H), 2.86 (t, J=9.0 Hz, 1H), 3.16 (t, J=9.5 Hz, 1H), 3.34-3.43 (m, 2H), 3.48-3.62 (m, 3H), 3.79 (s, 3H), 3.85 (d, J=9.5 Hz, 1H), 4.22 (m, 4H), 6.78 (d, J=8.5 Hz, 1H), 6.81-6.86 (m, 3H), 6.93-7.09 (m, 5H), 7.33-7.38 (m, 2H). MS (DCI) m/e 579 (M+H$^+$). Anal calcd for $C_{32}H_{35}ClN_2O_6 \cdot 1.1\ CH_3CO_2C_2H_5 \cdot 0.15\ H_3PO_4$: C, 63.30; H, 6.46; N, 4.06. Found: C, 63.54; H, 6.09; N, 3.98.

Example 472

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(4-pyridylmethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 2.84 (t, J=9.6 Hz, 1H), 2.88 (dd, J=9.6, 7.3 Hz, 1H), 3.09 (dd, J=3.3, 9.6 Hz, 1H), 3.21 (d, J=14.3 Hz, 1H), 3.53 (m, 1H), 3.78 (s, 3H), 3.81 (m, 2H), 5.92 (m, 2H), 6.73 (d, J=8.1 Hz, 1H), 6.82 (dd, J=1.8, 8.1 Hz, 1H), 6.93 (m, 2H), 6.95 (d, J=1.5 Hz, 1H), 7.43 (m, 4H), 8.44 (d, J=5.2 Hz, 2H). MS (DCI) m/e 433 (M+H$^+$). Anal calcd for $C_{25}H_{24}N_2O_5 \cdot 0.3\ CH_3CO_2C_2H_5$: C, 68.57; H, 5.80; N, 6.10. Found: C, 68.68; H, 5.60; N, 5.81.

Example 473

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-((N-butyl-N-(3-*tert*-butylphenylamino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 0.88 (t, J=7.2 Hz, 3H), 1.23 (s, 9H), 1.26-1.45 (m, 4H), 2.74 (dd, J=15.1 Hz, 1H), 2.84 (m, 1H), 3.13 (t, J=9.0 Hz, 1H), 3.29 (d, J=15.1 Hz, 1H), 3.50-3.66 (m, 4H), 3.77 (s, 3H), 3.84 (d, J=9.6 Hz, 1H), 5.92 (s, 2H), 6.74 (d, J=7.7 Hz, 1H), 6.79-6.85 (m, 4H), 6.86-6.90 (m, 1H), 6.99 (t, J=1.8 Hz, 1H), 7.06 (d, J=1.8 Hz, 1H), 7.13 (m, 2H), 7.33 (t, J=7.7 Hz, 1H), 7.42 (m, 1H). MS (DCI) m/e 587 (M+H$^+$). Anal calcd for $C_{35}H_{42}N_2O_6$: C, 71.65; H, 7.22; N, 4.77. Found: C, 71.56; H, 7.33; N, 4.69.

Example 474

<u>*trans,trans*-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-((N-butyl-N-(3-n-butylphenylamino)carbonyl)methyl)pyrrolidine-3-carboxylic acid</u>

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.88 (t, J=7.3 Hz, 3H), 0.92 (t, J=7.3 Hz, 3H), 1.23-1.59 (m, 8H), 2.58 (t, J=7.6 Hz, 2H), 2.75 (d, J=15.3 Hz, 1H), 2.80 (dd, J=8.5, 9.5 Hz, 1H), 3.12 (t, J=9.3 Hz, 1H), 3.29 (d, J=15.6 Hz, 1H), 3.46 (dd, J=4.9, 9.7 Hz, 1H), 3.52-3.64 (m, 3H), 3.78 (s, 3H), 3.83 (d, J=9.8 Hz, 1H), 5.92 (s, 2H), 6.74 (d, J=8.1 Hz, 1H), 6.79-6.87 (m, 4H), 7.05 (d, J=1.7 Hz, 1H), 7.10 (d, J=8.8 Hz, 2H), 7.20 (d, 7.8H), 7.29 (t, J=7.6 Hz, 1H). MS (DCI) m/e 587 ($M+H^+$). Anal calcd for $C_{35}H_{42}N_2O_6$: C, 71.65; H, 7.22; N, 4.77. Found: C, 71.33; H, 7.28; N, 4.74.

<u>Example 475</u>

<u>*trans,trans*-4-(3,4-Difluorophenyl)-2-(4-ethylphenyl)-1-(N-(n-butyl)-N-(3-methylphenyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid</u>

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.87 (t, 3H, J=7), 1.19 (t, 3H, J=7), 1.28 (m, 2H), 1.43 (m, 2H), 2.28 (s, 3H), 2.60 (q, 2H, J=7), 2.66 (m, 2H), 3.06 (m, 1H), 3.21 (d, 1H, J=15), 3.42 (dd, 1H, J=4,9), 3.58 (m, 3H), 3.71 (d, 1H, J=9), 6.80 (s, 2H), 7.06 (s, 4H), 7.18 (m, 4H), 7.45 (m, 1H). MS (APCI) m/e 535 $(M+H)^+$. Anal calcd for $C_{32}H_{36}N_2O_3F_2 \cdot 1.3$ HOAc: C, 67.83; H, 6.78; N, 4.57. Found: C, 67.83; H, 6.46; N, 4.70.

<u>Example 476</u>

<u>*trans,trans*-2-(4-Ethylphenyl)-4-(3,4-difluorophenyl)-1-(N-(n-butyl)-N-(3-chlorophenyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid</u>

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.82 (t, 3H, J=7), 1.16 (t, 3H, J=7), 1.23 (m, 2H), 1.35 (m, 2H), 2.55 (q, 2H, J=7), 2.66 (m, 2H), 3.01 (t, 1H, J=9), 3.16 (d, 1H, J=15), 3.32 (dd, 1H, J=4,9), 3.56 (m, 3H), 3.67 (d, 1H, J=9), 6.94 (d, 1H, J=7), 7.02 (m, 5H), 7.14 (m, 2H), 7.32 (m, 3H). MS (APCI) m/e 555 $(M+H)^+$. Anal calcd for $C_{31}H_{33}N_2O_3ClF_2 \cdot 0.6$ TFA: C, 61.88; H, 5.42; N, 4.48. Found: C, 61.90; H, 5.62; N, 3.98.

<u>Example 477</u>

<u>*trans,trans*-4-(1,4-Benzodioxan-6-yl)-2-(4-fluorophenyl)-1-(N-butyl-N-(3-chlorophenyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid</u>

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.87 (t, J=7 Hz, 3H), 1.10-1.30 (m, 4H), 2.60-2.75 (m, 2H), 3.03 (t, J=7 Hz, 1H), 3.15-3.75 (m, 6H), 4.02 (m, 4H), 6.75 (d, J=6 Hz, 1H), 6.85 (dd, J=7 Hz, 1H), 6.90 (7.19, J=m Hz, 6H), 7.32-7.43 (m, 3H). MS (DCI) m/e 567 $(M+H)^+$. Anal calcd for $C_{31}H_{32}N_2O_5FCl \cdot 1.6\ H_2O$: C, 62.49; H, 5.95; N, 4.70. Found: C, 62.20; H, 5.54; N, 4.42.

Example 478

<u>*trans,trans*-4-(Benzofuran-5-yl)-2-(4-ethylphenyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid</u>

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (t, 3H, J=7Hz), 0.84 (t, 3H, J=7Hz), 1.05 (q, 2H, J=7Hz), 1.21 (t, 3H, J=7Hz), 1.25 (m, 2H), 1.45 (m, 2H), 2.62 (q, 2H, J=7Hz), 2.80 (d, 1H, J=13Hz), 3.0 (m, 2H), 3.15 (m, 2H), 3.35 (m, 1H), 3.43 (m, 2H), 3.52 (m, 1H), 4.40 (m, 2H), 6.73 (d, 1H, J=1Hz), 7.14 (d, 2H, J=8Hz), 7.26 (s, 1H), 7.31 (d, 2H, J=8Hz), 7.44 (s, 2H), 7.60 (d, 1H, J=1Hz), 7.65 (s, 1H). MS (APCI) m/e 505 $(M+H)^+$. Anal. calc'd for $C_{31}H_{40}N_2O_4$: C, 73.78; H, 7.99; N, 5.55. Found: C, 73.69; H, 7.97; N, 5.21.

Example 479

<u>*trans,trans*-2-(4-Methoxy-3-fluorophenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-(pyrrolidine-1-carbonylmethyl)amino)ethyl]pyrrolidine-3-carboxylic acid</u>

Ethyl 2-(4-methoxy-3-fluorophenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[2-(N-propyl-aminoethyl]-pyrrolidine-3-carboxylate, prepared according to the procedures of Example 61B (300 mg), N-bromoacetyl pyrrrolidine (132 mg) and diisopropylethylamine (154 mg) were heated for 1 hour at 50 °C in 1 mL of acetonitrile to give the intermediate ethyl ester. The ester was hydrolyzed to the title compound by the method of Example 1D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J=7Hz, 3H), 1.30-1.45 (m, 2H), 1.75-1.92 (m, 4H), 2.30-2.40 (m, 1H), 2.47-2.58 (m, 2H), 2.70-3.00 (m, 5H), 3.24-3.45 (m, 6H), 3.50-3.70 (m, 2H), 3.83 (s, 3H), 3.86 (d, J=9Hz, 1H), 3.88 (s, 3H), 5.93 (s, 2H), 6.58 (d, J=2Hz, 1H), 6.70 (d, J=2Hz, 1H), 6.87 (t, J=8Hz, 1H), 7.10 (d, J=9Hz, 1H), 7.21 (dd, J=2Hz, 12Hz, 1H).

Example 480

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-((N-(perhydroazepinylcarbonyl)-(D)-leucyl)amino)ethyl)pyrrolidine-3-carboxylic acid

Example 480A

D-Leucine O-benzyl ester Tosylate salt

To benzyl alcohol (8.2 g) dissolved in benzene (30 mL) was added D-leucine (5.0 g) and *p*-toluenesulfonic acid monohydrate (8.0 g). The reaction was warmed to reflux with removal of water overnight. Once TLC indicated consumption of starting material, the reaction was cooled, and the resulting solid was filtered and washed with EtOAc to give the title compound as a white powder (14.26 g, 99%).

Example 480B

N-Perhydroazepinylcarbonyl-D-Leucine O-Benzyl ester

To the compound resulting from Example 480A (1.0 g) dissolved in chloroform (20 mL) was added triethylamine (0.4 mL). The solution was cooled to 0 °C, and carbonyldiimidazole was added. After 1.5 hours, TLC indicated complete consumption of starting material, so hexamethylene imine (0.327 mL) was added. After 1 hour, an additional amount of hexamethylene imine (0.330 mL) was added, and the reaction was stirred at ambient temperature overnight. The solution was washed with sodium bicarbonate (2 x 20 mL), 1 N H_3PO_4 (2 x 20 mL), and brine (20 mL), dried over Na_2SO_4, decanted and evaporated. The residue was purified by flash chromatography on silica gel eluting with 25 - 50% EtOAc in hexanes to give the title compound as a crystalline solid (0.835 g, 89%).

Example 480C

N-Perhydroazepinylcarbonyl-D-Leucine

To the compound resulting from Example 480B (200 mg) dissolved in dry ethanol (1.0 mL) was added 10% palladium on carbon (10 mg). After flushing the flask with nitrogen, the reaction was stirred vigorously under an atmosphere of hydrogen for 1 hour. The reaction was filtered through infusorial earth and evaporated to give the title compound (140 mg).

Example 480D

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(cyanomethyl)-pyrrolidine-3-carboxylic acid ethyl ester

To the compound resulting from Example 1C (510 mg of a 50 % wt. solution in toluene) dissolved in acetonitrile (2.0 mL) was added diisopropylethylamine (0.24 mL), followed by bromoacetonitrile (0.072 mL). After 2 hours, TLC indicated complete comsumption of starting material. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel eluting with 20 - 40% EtOAc in hexanes to give the title compound as a colorless oil (0.28 g, 99%).

Example 480E

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-aminoethyl)-pyrrolidine-3-carboxylic acid ethyl ester

To the compound resulting from Example 480D (275 mg) dissolved in 10 mL each of triethylamine and ethanol was added Raney nickel catalyst (0.2 g), and the reaction was placed under a hydrogen atmosphere (4 atmospheres) for 3 days. The reaction was filtered and evaporated. The residue was dissolved in methylene chloride (10 mL) and extracted with 1 M HCl (5 x 1 mL). The combined aqueous extracts were basified and then extracted with methylene chloride (5 x 2 mL). The combined organic extracts were dried with $MgSO_4$, filtered and evaporated to give the title compound as an unstable oil (0.14 g).

Example 480F

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-((N-(perhydroazepinylcarbonyl)leucyl)amino)ethyl)-pyrrolidine-3-carboxylic acid, ethyl ester

The compound resulting from Example 480E (0.10 g) was dissolved in methylene chloride (3.0 mL), and the compound resulting from Example 480C (0.07 g) was added. The solution was cooled to 0 °C, and EDCI (0.052 g) was added. After 4 hours, the reaction was evaporated and partitioned between water (1 mL), and EtOAc (10 mL). The orgainc solution was washed with water (1 mL) and brine (1 mL), dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography on silica gel eluting with 50 - 60% EtOAc in hexanes to give the title compound as a colorless oil (0.075 g, 48%).

Example 480G

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-((N-(perhydroazepinylcarbonyl)leucyl)amino)ethyl)pyrrolidine-3-carboxylic acid

The compound resulting from Example 480F (0.75 g) was dissolved in ethanol (1.0 mL) and 5 M NaOH (0.050 mL) was added. After 2 hours, additional 5 M NaOH (0.090 mL) was added. After an additional 3.5 hours, the reaction was evaporated. The residue was dissolved in water (5 mL) and washed with diethyl ether (2 x 2 mL). The aqueous solution was acidified with 1 N H_3PO_4 to pH 3. The solid which precipitated dissolved when the mixture was extracted with chloroform (3 x 3 mL). The chloroform extracts were washed with brine (2 mL), dried with $MgSO_4$, filtered and evaporated to give the title compound as a tan solid (0.053 g). Purification by HPLC (Vydac mC18) eluting with a 10 - 70% gradient of CH_3CN in 0.1%TFA provided suitable material (0.049 g) after lyophilization of the desired fractions. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.82 (dd, 6.4, 4.4 Hz, 6H), 0.87 (dd, J = 5.7, 5.7 Hz, 6H), 1.04-1.28 (m, 3H), 1.34-1.65 (m, 19H), 2.95 (br m, 2H), 3.15-3.40 (m, 14H), 3.40-3.55 (m, 4H), 3.58-3.68 (m, 2H), 3.70-3.76 (br m, 2H), 3.80 (s, 3H), 3.81 (s, 3H), 4.15 (br m, 2H), 5.10 (br m, 2H), 5.93 (s, 3H), 5.95 (s, 3H), 6.70-6.97 (m, 13H), 7.43-7.56 (br m, 3H), 8.2 (br s, 1H), 8.5 (br s, 1H). MS(DCI/NH_3) m/e 623 $(M+H)^+$. Anal calcd for $C_{34}H_{46}N_4O_7 \cdot 2.00$ TFA: C, 53.65; H, 5.69; N, 6.58. Found: C, 53.66; H, 5.66; N, 6.54.

Example 481

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(N,N-di(*n*-hexyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 0.80-0.95 (m, 6H), 1.0 (m, 2H), 1.07 (1.55, J=m Hz, 14H), 2.70 (d, J=13 Hz, 1H), 2.85-3.15 (m, 4H), 3.20-3.60 (m, 9H), 3.64 (d, J=10 Hz, 1H), 3.79 (s, 3H), 5.90 (m, 2H), 6.70 (d, 8H), 1, 6.80-6.93 (m, 3H), 7.05 (2, 1H), 7.35 (d, J=10 Hz, 2H). Anal calcd for $C_{33}H_{46}N_2O_6 \cdot 1.7\ H_2O$: C, 66.35; H, 8.34; N, 4.69. Found: C, 66.32; H, 8.04; N, 4.52.

Example 482

trans,trans-4-(1,4-Benzodioxan-6-yl)-2-(4-fluorophenyl)-1-(N-butyl-N-(3-methylphenyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 0.87 (t, J=7 Hz, 3H), 1.20-1.35 (m, 2H), 1.35-1.40 (m, 2H), 2.32 (s, 3H), 2.55-2.70 (m, 2H), 2.97 (t, J=7 Hz, 1H), 3.22 (d, J=14 Hz, 1H), 3.25-3.70 (m, 5H), 4.20 (m, 4H), 6.97 (d, J=2 Hz, 1H), 7.09 (m, 2H),

7.15-7.35 (m, 2H). MS (DCI) m/e 547 $(M+H)^+$. Anal calcd for $C_{32}H_{35}N_2O_5F \cdot 1.2\ H_2O$: C, 67.64; H, 6.63; N, 4.93. Found: C, 67.73; H, 6.37; N, 4.70.

Example 483

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(((N-butyl-N-(3-nitrobenzyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, $CDCl_3$) δ (rotamer) 8.14 (2H, m), 8.05 (7.83) (1H, m), 7.60-7.30 (3H, m), 7.13 (1H, m), 7.10-6.70 (5H, m), 5.94 (2H, m), 5.43 (5.33) (1H, d, J=12), 4.75 (1H, bd, J=15), 4.60-4.20 (2H, m), 4.10 (2H, m), 3.80 (3.76) (3H, s), 3.75-3.40 (3H, m), 3.20-2.80 (2H, m), 1.50 (1H, m), 1.30 (1H, m), 1.20-1.00 (2H, m), 0.91 (0.78) (3H, t, J=8). MS (DCI/NH_3) m/e 590 $(M+H^+)$. Anal calcd for $C_{32}H_{35}N_3O_8 \cdot 2.1$ TFA: C, 52.44; H, 4.51; N, 5.07. Found: C, 52.25; H, 4.83; N, 5.71.

Example 484

trans,trans-4-(1,2-Dihydrobenzofuran-5-yl)-2-(4-ethylphenyl)-1-(((N-butyl-N-(3,4-dimethoxybenzyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H (300MHz, $CDCl_3$) δ (rotamer) 7.40 (2H, m), 7.30-7.10 (4H, m), 6.90-6.70 (3H, m), 6.48 (1H, m), 5.45 (1H, m), 4.65 (1H, d, J=15), 4.57 (2H, dt, J=9, 3), 4.40-4.00 (5H, m), 3.87 (3.85) (3H, s), 3.84 (1H, m), 3.83 (3.79) (3H, s), 3.56 (2H, m), 3.20 (2H, t, J=10), 2.90 (1H, m), 2.64 (2H, q, J=8), 1.52 (1H, m), 1.31 (2H, m), 1.22 (3H, dt, J=9, 2), 1.07 (1H, m), 0.92 (0.78) (3H, t, J=8). MS (DCI/NH_3) m/e 601 $(M+H^+)$. Anal calcd for $C_{36}H_{44}N_2O_6 \cdot 1.35$ TFA: C, 61.59; H, 6.06; N, 3.71. Found: C, 61.69; H, 6.04; N, 3.63.

Example 485

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(((N-butyl-N-(4-heptyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 0.71-1.04 (m, 11H), 1.07-1.35 (m, 6H), 1.73-1.53 (m, 4H), 2.79-3.25 (m, 5H), 3.35-3.44 (m, 1H), 3.51-3.68 (m, 3H), 3.78-3.89 (m, 1H), 3.79 (s, 3H), 5.92 (m, 2H), 6.74 (dd, J=1.7, 8.1 Hz, 1H), 6.85 (td, J=1.7, 8.1 Hz, 1H), 6.93 (m, 2H), 7.02 (dd, J=1.7, 9.5 Hz, 1H), 7.36 (m, 2H). MS

(C.I.) m/e 553 ($M+H^+$). Anal calcd for $C_{32}H_{44}N_2O_6$: C, 69.54; H, 8.02; N, 5.07. Found: C, 69.31; H, 7.89; N, 5.06.

Example 486

trans,trans-2-(4-Methylcyclohexyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared and isolated as an amorphous solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (3H, d, J = 7Hz), 0.92 (3H, t, J = 7Hz), 0.96 (3H, t, J = 7Hz), 1.05 (1H, m), 1.22-1.40 (7H, m), 1.45-1.65 (6H, m), 1.67-1.84 (4H, m), 3.17-3.45 (6H, m), 3.70 (1H, brm), 3.82 (1H, dd, J = 9Hz, 15Hz), 3.86 (1H, d, J = 15Hz), 5.93 (2H, s), 6.73 (1H, d, J = 8Hz), 6.78 (1H, dd, J = 2Hz, 8Hz), 6.88 (1H, d, J = 2Hz). MS (DCI/NH_3) m/e 501 $(M+H)^+$. Anal calcd for $C_{29}H_{44}N_2O_5 \cdot 0.25\ CF_3CO_2H$: C, 66.96; H, 8.43; N, 5.29. Found: C, 66.79; H, 8.60; N, 4.87.

Example 487

trans,trans-2-(2-Propylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared and isolated as an amorphous solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85 (6H, m), 0.92 (3H, t, J = 7Hz), 0.97 (3H, t, J = 7Hz), 1.12-1.40 (13H, m), 1.42-1.68 (6H, m), 2.90 (1H, m), 3.14-3.30 (2H, m), 3.33 (4H, m), 3.72 (1H, brm), 3.90 (1H, brm), 5.93 (2H, dd, J = 2Hz, 4Hz), 6.73 (1H, d, J = 8Hz), 6.78 (1H, dd, J = 2Hz, 8Hz), 6.88 (1H, d, J = 2Hz). MS (DCI/NH_3) m/e 517 $(M+H)^+$. Anal calcd for $C_{30}H_{48}N_2O_5 \cdot 0.35\ CF_3CO_2H$: C, 66.24; H, 8.76; N, 5.03. Found: C, 66.26; H, 8.82; N, 4.98.

Example 488

trans,trans-4-(1,4-Benzodioxan-6-yl)-2-(4-fluorophenyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 0.83 (t, J=7 Hz, 3H), 0.89 (t, J=7 Hz, 3H), 0.90-1.17 (m, 4H), 1.20-1.65 (m, 5H), 2.77d (13, 1H), 2.87 (dd, J=8, 2 Hz, 1H), 2.95-3.60 (m, 7H), 3.71 (d, J=9 Hz, 1H), 4.21 (s, 4H), 6.72 (d, 1H), 6.91 (dd, J=8 Hz, 1H), 6.97 (d, J=2 Hz, 1H), 7.05 (t, J=7 Hz, 2H), 7.40-7.50 (m, 2H). MS (DCI) m/e 513

$(M+H)^+$. Anal calcd for $C_{29}H_{37}N_2O_5F \cdot 1.2C\ F_3COOH$: C, 58.07; H, 5.93; N, 4.31. Found: C, 57.94; H, 5.81; N, 4.56.

Example 489

trans,trans-2-(3-Methylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared and isolated as an amorphous solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.83 (3H, t, J = 7Hz), 0.85 (3H, d, J= 7Hz), 0.91 (3H, t, J = 7Hz), 0.97 (3H, t, J = 7Hz), 1.05-1.22 (2H, m), 1.22-1.41 (7H, m), 1.43-1.68 (5H, m), 1.89 (1H, m), 2.94 (1H, t, J = 6Hz), 3.15-3.27 (3H, m), 3.29-3.60 (5H, m), 3.72 (1H, brd, J = 6Hz), 3.92 (1H, brd, J = 13.5Hz), 5.93 (2H, dd, J = 2Hz, 4Hz), 6.73 (1H, d, J = 8Hz), 6.78 (1H, dd, J = 2Hz, 8Hz), 6.88 (1H, d, J = 2Hz). MS (DCI/NH_3) m/e 489 $(M+H)^+$. Anal calcd for $C_{28}H_{44}N_2O_5 \cdot 0.30\ CF_3CO_2H$: C, 65.70; H, 8.54; N, 5.36. Found: C, 65.93; H, 8.81; N, 4.84.

Example 490

trans,trans-2-(2-Ethylbutyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared and isolated as an amorphous solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85 (6H, m), 0.92 (3H, t, J = 7Hz), 0.97 (3H, t, J = 7Hz), 1.13-1.41 (13H, m), 1.43-1.72 (6H, m), 2.96 (1H, brm), 3.12-3.52 (6H, m), 3.55-3.70 (1H, m), 3.70-3.86 (2H, m), 3.99 (1H, brm), 5.93 (2H, dd, J = 2Hz, 4Hz), 6.73 (1H, d, J = 8Hz), 6.78 (1H, dd, J = 2Hz, 8Hz), 6.88 (1H, d, J = 2Hz). MS (DCI/NH_3) m/e 489 $(M+H)^+$. Anal calcd for $C_{28}H_{44}N_2O_5 \cdot 0.45\ CF_3CO_2H$: C, 64.28; H, 8.30; N, 5.19. Found: C, 64.16; H, 8.38; N, 5.08.

Example 491

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-isobutyl-N-(butanesulfonylamino))ethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared. ^1H NMR (CD_3OD, 300 MHz) δ 0.74 (d, 3H, J=7), 0.83 (d, 3H, J=7), 0.94 (t, 3H, J=7), 1.44 (hex, 2H), 1.67 (m, 4H), 2.91 (d, 2H, J=8), 3.04 (dd, 2H, J=8,10), 3.1-3.6 (m, 5H), 3.78 (m, 2H), 3.92 (s, 3H), 4.60 (m, 1H), 5.97 (s, 2H), 6.82 (d, 1H,

J=8), 6.89 (dd, 1H, J=2, 8), 7.01 (d, 1H, J=2), 7.22 (t, 1H, J=9), 7.39 (m, 2H). MS (ESI) m/e 579 $(M+H)^+$.

Example 492

trans,trans-2-(4-Methoxy-3-fluorophenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-[4-ethylpyrimidin-2-yl]amino)ethyl]pyrrolidine-3-carboxylic acid

1-Dimethylamino-1-pentene-3-one, prepared by the method described in Syn. Comm. 12 (1), 35 (1982), was converted to 2-amino-4-ethylpyrimidine with guanidine by the method of Chem. Ber. 97, 3397 (1964). This material was converted to 2-bromo-4-ethyl-pyrimidine with $NaNO_2$ and HBr, using the method of Helv. Chim. Acta 75, 1629 (1992). This bromopyrimidine was reacted with ethyl 2-(4-methoxphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propylamino)propyl]-pyrrolidine-3-carboxylate, prepared using the procedures of Example 61B, using the procedure for Example 418, to give the title compound as a white powder. ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, J=7Hz, 3H), 1.11 (t, J=7Hz, 3H), 1.45 (sextet, J=7Hz, 2H), 2.18-2.27 (m, 1H), 2.45 (q, J=7Hz, 2H), 2.80-2.97 (m, 3H), 3.40-3.75 (m, 7H), 3.83 (s, 3H), 5.95 (s, 2H), 6.25 (d, J=4Hz, 1H), 6.68 (d, J=8Hz, 1H), 6.79 (dd, J=2Hz, 8Hz, 1H), 6.82 (t, J=9Hz, 1H), 6.92 (d, J=2Hz, 1H), 7.05 (d, J=9Hz, 1H), 7.15 (dd, J=2Hz, 12Hz, 1H), 8.10 (d, J=4Hz, 1H).

Example 493

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-((N-butyl-N-(3,4-dimethylphenyl)aminocarbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, CD_3OD) δ 0.87 (t, J=7.3 Hz, 3H), 1.23-1.36 (m, 2H), 1.38-1.43 (m, 2H), 2.22 (s, 3H), 2.29 (s, 3H), 2.79 (d, J=14.9 Hz, 1H), 2.84 (dd, J=8.6, 9.7 Hz, 1H), 3.16 (t, J=9.5 Hz, 1H), 3.32 (d, J=15.3 Hz, 1H), 3.43-3.61 (m, 4H), 3.79 (s, 3H), 3.88 (d, J=9.8 Hz, 1H), 5.93 (s, 2H), 6.74 (m, 3H), 6.83 (m, 3H), 7.04 (d, J=1.7 Hz, 1H), 7.11 (m, 3H). MS (C.I.) m/e 559(MH^+). Anal calcd for $C_{33}H_{38}N_2O_6 \cdot 0.3H_2O$: C, 70.27; H, 6.90; N, 4.97. Found: C, 70.24; H, 6.62; N, 4.58.

Example 494

trans,trans-2-(3-Methylpent-3-en-1-yl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedure described in Example 1, the title compound was prepared and isolated as an amorphous solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (3H, t, J = 7Hz), 0.97 (3H, t, J = 7Hz), 1.22-1.40 (5H, m), 1.44-1.61 (8H, m), 1.82 (1H, brm), 2.02 (2H, m), 3.05-3.30 (4H, m), 3.3.8 (1H, m), 3.55 (1H, brm), 3.85 (2H, m), 4.12 (1H, brd, J = 15Hz), 5.11 (1H, dd, J = 6Hz, 12Hz), 5.93 (2H, s), 6.73 (1H, d, J = 8Hz), 6.78 (1H, dd, J = 2Hz, 8Hz), 6.88 (1H, d, J = 2Hz). MS (DCI/NH_3) m/e 487 $(M+H)^+$. Anal calcd for $C_{28}H_{42}N_2O_5 \cdot 0.7\ CF_3CO_2H$: C, 62.34; H, 7.60; N, 4.95. Found: C, 62.49; H, 7.43; N, 4.73.

Example 495
1-(N-Phenylaminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Example 495A
N-Phenylbromoacetamide

To a stirred solution of aniline (7.40 mmol) in methylene chloride (25 mL) at -50 °C was added successively N,N-diisopropylethylamine (1.58 mL, 8.14 mmol, 1.1 eq) and bromoacetyl bromide (0.72 mL, 7.40 mmol, 1 eq) such that the temperature did not exceed -40 °C. On completion of the addition, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. After stirring for a further 30 minutes, the mixture was diluted with ether (70 mL) and poured into 1 N sodium bisulfate solution. The phases were separated, and the upper layer was washed successively with water and brine. The organic phase was dried (Na_2SO_4) and the solvent evaporated to half volume, at which point the product crystallized. The crystals were removed by vacuum filtration to afford the title compound.

Example 495B
trans,trans-1-(N-Phenylaminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1 and the compound resulting from Exampe 495A, the title compound was prepared. ^1H NMR (300 MHz, $CDCl_3$) δ 8.8 (bs, 1H) 7.49 (2H, d, *J*=8Hz), 7.38 (4H, m), 7.11 (1H, tt, *J*=8&2Hz), 6.99 (1H, d, *J*=2Hz), 6.91 (2H, d, *J*=8Hz), 6.86 (1H, d, *J*=2Hz), 6.81 (1H, d, *J*=8Hz), 5.99 (1H, d, *J*=2Hz), 5.98 (1H, d, *J*=2Hz), 3.94 (1H, d, *J*=10Hz), 3.78 (3H, s), 3.70 (1H, ddd, *J*=6, 5&3Hz), 3.42 (1H, dd, *J*=10&3Hz), 3.41 (1H, d, *J*=16Hz), 3.18 (1H, dd,

J=11&9Hz), 3.01 (1H, t, J=10Hz), 2.93 (1H, d, J=16Hz). MS (DCI, NH_3) m/e 475 ($M+H^+$). Anal. Calc for $C_{27}H_{26}N_2O_6 \cdot 1\ H_2O$: C, 65.85, H, 5.73, N 5.69, Found: C, 65.95, H, 5.52, N, 5.38.

Example 496

trans,trans-1-(N-(2,3-Dimethylphenyl)aminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, $CDCl_3$) δ 8.68 (1H, bs), 7.64 (d, J=8Hz), 7.38, (2H, d, J=8Hz), 7.09 (1H, t, J=8Hz), 6.97, (1H, d, J=8Hz), 6.90 (1H, d, J=2Hz), 6.88 (2H, d, J=8Hz), 6.82 (1H, dd, J=8&3Hz), 6.76 (1H, d, J=8Hz), 5.97 (1H, d, J=2Hz), 5.96 (1H, d, J=2Hz), 3.95 (1H, d, J=10Hz), 3.80 (3H, s), 3.70 (1H, ddd, J=6, 5&3Hz), 3.48 (1H, dd, J=10&3Hz), 3.44 (1H, d, J=16Hz), 3.18 (1H, dd, J=11&9Hz), 3.06 (1H, t, J=10Hz), 2.96 (1H, d, J=16Hz), 2.31 (3H, s), 2.16 (3H, s). MS (DCI, NH_3) m/e 503 ($M+H^+$). Anal. Calc for $C_{29}H_{30}N_2O_6 \cdot 0.5\ H_2O$: C, 68.09, H, 6.11, N, 5.48. Found: C, 68.13, H, 5.91, N, 5.29.

Example 497

trans,trans-1-(N-(2,4-Dimethylphenyl)aminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, $CDCl_3$) δ 8.60 (1H, bs), 7.78 (d, J=8Hz), 7.38, (2H, d, J=8Hz), 6.99 (1H, m), 6.95, (1H, d, J=8Hz), 6.94 (1H, d, J=2Hz), 6.88 (2H, d, J=8Hz), 6.82 (1H, dd, J=8&3Hz), 6.77 (1H, d, J=8Hz), 5.97 (1H, d, J=2Hz), 5.96 (1H, d, J=2Hz), 3.92 (1H, d, J=10Hz), 3.79 (3H, s), 3.68 (1H, ddd, J=6, 5&3Hz), 3.43 (1H, dd, J=10&3Hz), 3.42 (1H, d, J=16Hz), 3.18 (1H, dd, J=11&9Hz), 3.04 (1H, t, J=10Hz), 2.95 (1H, d, J=16Hz), 2.29 (3H, s), 2.24 (3H, s). MS (DCI, NH_3) m/e 503 ($M+H^+$). Anal. Calc for $C_{29}H_{30}N_2O_6 \cdot 0.75\ H_2O$: C, 67.50, H, 6.15, N 5.43. Found: C, 67.42; H, 5.95; N, 5.13.

Example 498

trans,trans-1-(N-(2,5-Dimethylphenyl)aminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, $CDCl_3$) δ 8.62 (1H, bs), 7.79 (1H, bs), 7.38, (2H, d,

J=8Hz), 7.03 (1H, d, *J*=8Hz), 6.95, (1H, d, *J*=8Hz), 6.94 (1H, d, *J*=2Hz), 6.88 (2H, d, *J*=8Hz), 6.82 (1H, dd, *J*=8&3Hz), 6.77 (1H, d, *J*=8Hz), 5.97 (2H, s), 3.92 (1H, d, *J*=10Hz), 3.78 (3H, s), 3.70 (1H, ddd, *J*=6, 5&3Hz), 3.48 (1H, dd, *J*=10&3Hz), 3.42 (1H, d, *J*=16Hz), 3.18 (1H, dd, *J*=11&9Hz), 3.04 (1H, t, *J*=10Hz), 2.95 (1H, d, *J*=16Hz), 2.29 (3H, s), 2.24 (3H, s). MS (DCI, NH_3) m/e 503 ($M+H^+$). Anal. Calc for $C_{29}H_{30}N_2O_6 \cdot 0.5\ H_2O$: C, 68.09; H, 6.11; N, 5.48. Found: C, 67.72; H, 5.89; N, 5.25.

Example 499

trans,trans-1-(N-(3,4-Dimethylphenyl)aminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, $CDCl_3$) δ 8.73 (1H, bs), 7.38 (2H, bd, *J*=8Hz), 7.30, (1H, d, *J*=3Hz), 7.20 (1H, bs), 7.08, (1H, d, *J*=8Hz), 7.01 (1H, bs), 6.90 (2H, d, *J*=8Hz), 6.85 (1H, bs), 6.80 (1H, d, *J*=8Hz), 5.99 (1H, d, *J*=3Hz), 5.98 (1H, d, *J*=3Hz), 3.92 (1H, d, *J*=10Hz), 3.78 (3H, s), 3.70 (1H, ddd, *J*=6, 5&3Hz), 3.48 (1H, dd, *J*=10&3Hz), 3.42 (1H, d, *J*=16Hz), 3.18 (1H, dd, *J*=11&9Hz), 3.04 (1H, t, *J*=10Hz), 2.95 (1H, d, *J*=16Hz), 2.25 (3H, s), 2.21 (3H, s). MS (DCI, NH_3) m/e 503 ($M+H^+$). Anal. Calc for $C_{29}H_{30}N_2O_6 \cdot 0.75\ H_2O$: C, 67.50; H, 6.15; N 5.43. Found: C, 67.24; H, 5.94; N, 5.20.

Example 500

trans,trans-1-(N-(3,5-Dimethylphenyl)aminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H NMR (300 MHz, $CDCl_3$) δ 8.75 (1H, bs), 7.35, (2H, d, *J*=8Hz), 7.10 (2H, s), 7.02 (1H, d, *J*=3Hz), 6.90 (2H, d, *J*=8Hz), 6.84 (1H, d, *J*=2Hz), 6.80, (1H, d, *J*=8Hz), 6.76 (1H, bs), 5.99 (1H, d, *J*=3Hz), 5.98 (1H, d, *J*=3Hz), 3.92 (1H, d, *J*=10Hz), 3.79 (3H, s), 3.68 (1H, ddd, *J*=6, 5&3Hz), 3.40 (2H, m), 3.18 (1H, dd, *J*=11&9Hz), 2.98 (1H, t, *J*=10Hz), 2.88 (1H, d, *J*=16Hz), 2.3 (6H, s). MS (DCI, NH_3) m/e 503 ($M+H^+$). Anal. Calc for $C_{29}H_{30}N_2O_6 \cdot 0.5\ H_2O$: C, 68.09; H, 6.11; N 5.48. Found: C, 67.93; H, 6.01; N, 5.19.

Example 501

Alternate Preparation of

(+)-*trans,trans*-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid Hydrochloride Salt

Example 501A

N, N-Dibutyl bromoacetamide

To a solution of bromoacetyl bromide (72.3 mL, 830 mmol) in toluene (500 mL) cooled to 0 °C was added a solution of dibutylamine (280.0 mL, 1.66 mol) in toluene (220 mL) via an addition funnel maintaining the reaction temperature below 10 °C. Upon completion of the addition, the reaction mixture was stirred at 0 °C for 15 minutes. A solution of 2.5% aqueous H_3PO_4 (500 mL) was slowly introduced, and the reaction mixture was allowed to warm to room temperature with vigorous stirring. The solution is 2.5% phosphoric acid by weight. The layers were separated and the organic phase washed with water (500 mL) and concentrated to provide the bromoacetamide as a solution in toluene.

Example 501B

5-(2-Nitrovinyl)-1,3-benzodioxole

To piperonal (15.55 kg, 103.5 mol) under mechanical stirring and under nitrogen was added ammonium acetate (13.4 kg, 173.8 mol), acetic acid (45.2 kg), and nitromethane (18.4 kg, 301.4 mol) sequentially. The mixture was warmed to 70 °C. After about 30 minutes, the yellow product began to crystallize. The reaction temperature was raised to 80 °C and stirred for about 10 hours until minimal piperonal remains. The somewhat thick reaction mixture was cooled to 10 °C and filtered. The precipitate was washed with acetic acid (2 x 8 kg) and then water (2 x 90 kg). The product was dried under a nitrogen purge and then in a vacuum oven at 50 °C for 2 days to afford 15.94 kg (80%) of the title compound as a bright yellow solid.

Example 501C

4-Methoxybenzoyl acetate

To potassium t-amylate (25 wt %, 50.8 kg, 99.26 mol) in toluene (15.2 kg) cooled to 5 °C under mechanical stirring and under nitrogen was added a mixture of 4-methoxyacetophenone (6.755 kg, 44.98 mol) and diethyl carbonate (6.40 kg, 54.18 mol) in toluene over 1 hour maintaining the temperature below 10 °C. The reaction mixture was heated to 60 °C for 8 hours until no 4-methoxyacetophenone was detected by HPLC. The mixture was cooled to 20 °C and quenched by adding

to a mixture of acetic acid (8 kg) and water (90 kg) over 30 minutes while maintaining the temperature at <20 °C. The layers were separated, and the organic layer was washed with 5% sodium bicarbonate solution (41 kg) and concentrated to 14.65 kg. The temperature is maintained below 50 °C during the distillation. The yellow product concentrate was assayed by HPLC against an external standard and the yield was found to be 9.40 kg (94%).

Example 501D

Ethyl 2-(4-methoxybenzoyl)-4-nitromethyl-3-(1,3-benzodioxol-5-yl) butyrate

To the compound resulting from Example 501B (7.5 kg, 37.9 mol) suspended in THF (56 kg) with mechanical stirring under nitrogen was added the compound resulting from Example C (8.4 kg, 37.9 mol). The mixture was cooled to 17 °C, sodium ethoxide (6.4 g, 0.095 mol) was added, and the reaction was stirred for 30 minutes. After about 15 minutes, the nitrostyrene was completely dissolved. Sodium ethoxide (6.4 g, 0.095 mol) was added, and the mixture was stirred at 25 °C until HPLC shows less than 1 area % ketoester remaining. The reaction was concentrated to 32.2 kg which was determined by HPLC assay to be ~14.9 kg (95%).

Example 501E

Ethyl *cis, cis*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl) pyrrolidine-3-carboxylate

Raney nickel (20.0 g), from which the water had been decanted, was charged to a stirred hydrogenator equipped with a thermocouple. THF (20 mL), the crude compound resulting from Example 501D (40.82 g, 0.0482 mol), and acetic acid (2.75 mL, 0.0482 mol) were added sequentially. The mixture was put under a hydrogen atmosphere at 60 psi until the hydrogen uptake slowed dramatically. TFA was added, and the mixture was hydrogenated at 200 psi until HPLC shows no residual imine and <2 area % nitrone. The catalyst was filtered away and washed with 100 mL of methanol. The filtrate was assayed by HPLC and found to contain 13.3 g (75% yield) of the cis, cis-pyrrolidine compound. The filtrate was concentrated and chased with additional THF (200 mL) to give a final volume of 100 mL. The mixture was neutralized with 2 N NaOH solution (50 mL), diluted with water (200 mL), and extracted with ethyl acetate (2 x 100 mL). The combined nearly colorless ethyl acetate layers were assayed against an external standard by HPLC to be13.0 g (73%) of the title compound.

Example 501F

Ethyl *trans, trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl) pyrrolidine-3-carboxylate

The solution of the compound resulting from Example 501E (38.1 g, 0.103 mol) was chased with ethanol (200 mL) to a final volume of 100 mL and sodium ethoxide (3.40 g, 0.050 mol) was added. The mixture was heated to 75 °C. When HPLC shows <3% of the cis,cis isomer remaining, the mixture was cooled to room temperature. The product was assayed by HPLC against an external standard and found to contain 34.4 g (90% yield) of the title compound. The crude compound solution was concentrated and the residue taken up in isopropyl acetate (400 mL). The organic layer was washed with water (2 x 150 mL) and then extracted with 0.25 M phosphoric acid solution (2 x 400 mL). The combined phosphate layers were stirred with ethyl acetate (200 mL) and neutralized to pH 7 with solid sodium bicarbonate (21 g). The organic layer was separated and found to contain 32.9 g (87%) of the title compound.

Example 501G

Ethyl (2R,3R, 4S)-(+)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl) pyrrolidine-3-carboxylate, (S)-(+) mandelate salt

The solution resulting from Example 501F was chased with acetonitrile (100 mL) to give a final volume of 50 mL. (*S*)-(+)-Mandelic acid (2.06 g, 0.0136 mmol) was added and allowed to dissolve. The mixture was seeded with the product and allowed to stir at room temperature for 16 hours. The reaction mixture was cooled to 0 °C and stirred for 5 hours. The product was filtered and dried in a vacuum oven with a nitrogen purge for 1 day at 50 °C to give 5.65 g (40%) of the title compound. The purity of the product can be determined by chiral HPLC using Chiralpak AS, isocratic elution with 95:5:0.05 hexane-ethanol-diethylamine; flow - 1 mL/min.; UV detection at 227 nm. Retention times: (+)-enantiomer: 15.5 min.; (-)-enantiomer: 21.0 min.

Example 501H

(2R,3R,4S)-(+)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)- pyrrolidine-3-carboxylic acid

The compound resulting from Example 501G (20.0 g, 0.0383 mol) was suspended in ethyl acetate (150 mL) and 5% sodium bicarbonate solution (150 mL). The mixture was stirred at room temperature until the salt dissolved and carbon

dioxide evolution had ceased. The organic layer was separated and concentrated. The residue was chased with acetonitrile (200 mL) to a final volume of 100 mL and cooled to 10 °C. Diisopropylethylamine (11.8 mL, 0.0574 mol) and the compound resulting from Example A (10.5 g, 0.0421 mol) were added, and the mixture was stirred for 12 hours at room temperature. The reaction mixture was concentrated and chased with ethanol (200 mL) to a final volume of 100 mL. Sodium hydroxide solution (40%, 20 mL, 0.200 mol) was added, and the mixture was heated at 60 °C for 4 hours until HPLC showed no starting material remaining. The reaction mixture was poured into water (400 mL) and washed with hexanes (2 x 50 mL). The aqueous layer was washed with hexane (2 x 20 mL). A stirred mixture of the aqueous layer and ethyl acetate (400 mL) was neutralized to pH 5 with concentrated HCl (12 mL). The organic layer was separated and found to contain 18.3 g (94% yield) of the title compound.

Example 501I

(2R,3R,4S)-(+)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)- pyrrolidine-3-carboxylic acid hydrochloride salt

To a solution of the compound of Example 501H in ethyl acetate at room temperature in a mechanically stirred vessel equipped with a thermocouple, was added 39.4 mL of 1 N HCl in ethanol (0.0394 mol) The resultant solution was filtered to remove foreign matter, concentrated in vacuo, and chased with ethyl acetate (400 mL). The solution was seeded repeatedly, as the solvent was removed, until crystallization was initiated. The mixture was concentrated to a volume of 100 mL, and the product was filtered and washed with ethyl acetate (25 mL). The resultant white solid was dried in a vacuum oven under a nitrogen purge at 50 °C to afford 17.6 g (90%) of the title compound.

Example 502

trans, trans-2-(2-Methylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 502A

(±)-Ethyl 3-methylhexanoate

To a slurry of 60% sodium hydride (2.26g, 57 mmol) in 10mL of hexanes and 100mL of diethyl ether was added triethylphosphonoacetate (10.3mL, 52mmol).

Once gas evolution ceased, 2-pentanone (6.0mL, 64mmol) was added. After 3 hours at room temperature, the reaction was quenched with water, and partitioned into ether. The organic layer was washed with water and brine, dried with anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The residue was dissolved in 50mL of ethanol and 10% palladium on carbon (6.0g) was added. The vessel was pressurized to 4 atmosphere of hydrogen, and was shaken at room temperature for 3 hours. The reaction was filtered and the solvent was removed under reduced pressure to give 3.0g of the title compound.

Example 502B

(±)-Ethyl 5-methyl-3-oxooctanoate

To a solution of ethyl 3-methylhexanoate in 150mL of ethanol was added sodium hydroxide (2.3g, 57.6mmol). After 48 hours at room temperature, solvent was removed under reduced pressure, and the residue was dissolved in 150mL of water. The solution was washed with ether, then acidified with concentrated hydrochloric acid and washed with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure to give 2.7g of the corresponding acid from which 3.9g of the title compound was prepared by the method of Bram and Vilkas, *Bul. Chem. Soc. Fr.*, 945 (1964).

Example 502C

trans, trans-2-(2-Methylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1 and substituting ethyl 5-methyl-3-oxooctanoate for ethyl (4-methoxybenzoyl)acetate afforded the title compound, which was isolated by lyophilization from dilute aqueous TFA/CH_3CN. Note that the multiplicity of the signals in the aryl region of the NMR spectrum reflects a 1:1 mixture of diastereomers on the alkyl chain. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.8-1.0 (m, 12H), 1.2-1.4 (m, 7H), 1.45-1.6 (m, 6H), 1.6-1.74 (m, 1H), 1.8-2.0 (m, 1H), 3.1-3.4 (m, 5H), 3.67-3.78 (m, 1H), 3.8-3.91 (m, 1H), 4.0-4.2 (m, 2H), 4.3-4.5 (m, 2H), 5.93 (d, J=1.5 Hz, 2H), 6.73 (dd, J=8.1, 1.2 Hz, 1H), 6.79 (ddd, J=7.8, 1.8, 1.8 Hz,

1H), 6.86 (dd, J=3.9, 1.5 Hz, 1H). MS (DCI/NH_3) m/e 489 $(M+H)^+$. Anal calcd for $C_{28}H_{44}N_2O_5$• 1.0 TFA• 0.5 H_2O: C, 58.91; H, 7.58; N, 4.58. Found: C, 58.91; H, 7.58; N, 4.45.

Example 503

trans, trans-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Ethyl 3,3-dimethylhexanoate was prepared using the general procedure of Cahiez *et al.*, Tetrahedron Lett., 31, 7425 (1990). Using the procedures described in Example 502 and substituting ethyl 3,3-dimethylhexanoate for ethyl 3-methylhexanoate afforded the title compound, which was isolated by lyophilization from dilute aqueous TFA/CH_3CN. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.80-0.99 (m, 15H), 1.10-1.37 (m, 8H), 1.43-1.58 (m, 4H), 1.77-1.97 (m, 2H), 3.48-3.12 (m, 5H), 3.60-3.69 (m, 1H), 3.75-3.86 (m, 1H), 3.95-4.16 (m, 2H), 4.28-4.4 (m, 2H), 5.94 (s, 2H), 6.74 (d, J=7.8 Hz, 1H), 6.8 (dd, J=8.1, 1.5 Hz, 1H), 6.87 (d, J=1.8 Hz, 1H). MS (DCI/NH_3) m/e 503 $(M+H)^+$. Anal calcd for $C_{29}H_{46}N_2O_5$• 1.05 TFA: C, 60.01; H, 7.62; N, 4.50. Found: C, 60.21; H, 7.37; N, 4.33.

Example 504

trans,trans-2-(2-(1,3-Dioxo-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 504A

Ethyl 5-(1,3-dioxolyl)-3-oxopentanoate

The title compound was synthesized from ethyl acetoacetate and 2-bromomethyl-1,3-dioxane, according to the procedure of Huckin and Weiler, Tetrahedron Lett. 3927, (1971).

Sodium hydride 4.97 g (0.124 mol), as a 60% mineral oil dispersion, was weighed into a 250 mL flask, into which 80 ml of tetrahydrofuran was directly added. The flask was capped with septum cap, flushed with nitrogen, and cooled in an ice bath. To above stirred slurry was added dropwise 15.0 mL (0.118 mol) ethyl acetoacetate. After the addition was complete, the resulting mixture was stirred at 0 °C for additional 10 min. To above mixture was then added 48.4 mL (0.121 mol) *n*-

butyl lithium, a 2.50 M solution in hexane, in a dropwise manner. The resulting orange color solution was stirred for 10 min before 13.5 mL (0.130 mol) bromomethyl-1,3-dioxane was added in one portion. The reaction mixture was then allowed to warm to room temperature and stirred for additional 120 min before it was then quenched by slow addition of 9.8 ml (ca. 0.12 mol) concentrated hydrochloric acid. The biphasic mixture was poured to 50 ml of water and extracted with 150 ml of ethyl ether. The aqueous layer was extracted thoroughly with additional ethyl ether. The ethereal extracts were combined, washed with 2x50 ml of saturated brine, dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to give an brown oily residue. The crude product was purified using silica gel flash chromatography eluting with 20% ether/hexane to give 5.40 g (20%) of b-keto ester as a light yellow oil.

Example 504C

trans,trans-2-(2-(1,3-Dioxo-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 502 and substituting ethyl 5-(1,3-dioxolyl)-2-oxopentanoate for ethyl 3-methylhexanoate afforded the title compound. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, J = 7.2 Hz, 3H), 0.95 (t, J = 7.2 Hz, 3H), 1.23-1.38 (m, 4H), 1.52 (sextet, J = 7.9 Hz, 4H), 1.85-1.95 (m, 2H), 2.02-2.17 (m, 2H), 3.18 (dd, J = 6.0 Hz, 9.0 Hz, 2H), 3.30 (dd, J = 9.0 Hz, 18.0 Hz, 2H), 3.35 (m, 1H), 3.79 (dd, J = 3.6 Hz, 6.9 Hz, 1H), 3.83-3.88 (m, 3H), 3.97 (dd, J = 4.8 Hz, 6.0 Hz, 1H), 4.05 (q, J = 9.6 Hz, 2H), 4.30-4.40 (m, 1H), 4.37 (s, 2H), 4.87 (t, J = 3.6 Hz, 1H), 5.94 (s, 2H), 6.73 (d, J = 8.1 Hz, 1H), 6.79 (dd, J = 1.8 Hz, 8.1 Hz, 1H), 6.87 (d, J = 1.8 Hz, 1H). MS (APCI) $(M+H)^+$ at m/e 505. Anal calcd for $C_{27}H_{40}N_2O_7 \cdot 1.2$ TFA: C, 55.05; H, 6.47; N, 4.37. Found: C, 55.12; H, 6.44; N, 4.27.

Example 505

trans,trans-2-(2-(2-Tetrahydro-2*H*-pyran)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 505A

Ethyl 5-(2-tetrahydro-2*H*-pyran)-3-oxopentanoate

Using the procedure of Huckin and Weiler, Tetrahedron Lett. 3927, (1971), the title compound was prepared from ethyl acetoacetate and 2-(bromomethyl)tetrahydro-2*H*-pyran as a light yellow oil.

Example 505B

trans,trans-2-(2-(2-Tetrahydro-2*H*-pyran)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 502 and substituting ethyl 5-(2-tetrahydro-2*H*-pyran)-2-oxopentanoate for ethyl 3-methylhexanoate afforded the title compound as an amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz) as a mixture of two diastereoisomers: δ 0.89 (t, J = 8.1 Hz, 3H), 0.89 (t, J = 8.1 Hz, 3H), 0.91 (t, J = 8.1 Hz, 3H), 0.91 (t, J = 8.1 Hz, 3H), 1.20-1.40 (m, 10H), 1.42-1.66 (m, 18H), 1.71 (brm, 2H), 1.85 (brm, 2H), 1.96-2.23 (brm, 4H), 3.10-3.29 (m. 8H), 3.29-3.52 (m, 6H), 3.54-3.81 (m, 6H), 4.01 (q, J = 9 Hz, 2H), 4.12-4.25 (m, 4H), 4.43 (d, J = 9 Hz, 2H), 4.50 (d, J = 2.7 Hz, 2H), 5.94 (s, 2H), 5.95 (s, 2H), 6.76 (s, 2H), 6.76 (s, 2H), 6.81 (s, 1H), 6.81 (s, 1H). MS (APCI) $(M+H)^+$ at m/e 517. Anal calcd for $C_{29}H_{44}N_2O_6 \cdot 1.4$ TFA: C, 56.48; H, 6.77; N, 4.14. Found: C, 56.46; H, 6.99; N, 3.83.

Example 506

trans, trans-2-(2,2,4-Trimethyl-3-pentenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 506A

Methyl 3,3,5-trimethyl-4-hexenoate

To a slurry of isopropyltripenylphosphonium iodide (20.5g, 47mmol) in 200mL of tetrahydrofuran was added n-butyllithium (27mL of a 1.6M solution in hexane, 43mmol), and the solution was briefly warmed to 0°C. After recooling, a solution of methyl 3,3-dimethyl-4-oxobutenoate (5.7g, 40mmol), prepared according to the procedure of Hudlicky *et al.*, Synth. Commun., 16 169 (1986) in 10mL of tetrahydrofuran was added, and the reaction was warmed to 0°C for 30min. The reaction was quenched with dilute hydrochloric acid, and partitioned with ethyl acetate. The organic layer was washed with water, and brine, dried with anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure.

The residue was purified by flash chromatography on silica gel eluting with 10% ethyl acetate in hexanes to give 2.1g (30%) of the title compound.

Example 506B

trans, trans-2-(2,2,4-Trimethyl-3-pentenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 502 and substituting methyl 3,3,5-trimethyl-4-hexenoate for ethyl 3-methylhexanoate afforded the title compound, which was isolated by lyophilization from dilute aqueous TFA/CH_3CN. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, J=7.2 Hz, 3H), 0.94 (t, J=7.2 Hz, 3H), 1.11 (s, 3H), 1.13 (s, 3H), 1.24-1.37 (m, 4H), 1.46-1.59 (m, 4H), 1.61 (d, J=1.2 Hz, 3H), 1.69 (d, J=1.2 Hz, 3H), 2.04-2.11 (m, 2H), 3.10-3.20 (m, 2H), 3.30-3.39 (m, 3H), 3.67-3.82 (m, 2H), 3.95-4.08 (m, 1H), 4.32 (m, 2H), 4.37-4.47 (m, 1H), 4.99 (s, 1H), 5.95 (s, 2H), 6.73 (d, J=7.8 Hz, 1H), 6.78 (dd, J=8.4, 1.2 Hz, 1H), 6.84 (d, J=1.2 Hz, 1H). MS (DCI/NH_3) m/e 515 $(M+H)^+$. Anal calcd for $C_{30}H_{46}N_2O_5$• 1.05 TFA: C, 60.77; H, 7.48; N, 4.42. Found: C, 60.83; H, 7.20; N, 4.43.

Example 507

trans, trans-2-(2,2,-Dimethyl-2-(1,3-dioxolan-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 507A

Methyl 3,3-dimethyl-3-(1,3-dioxolan-2-yl)propanoate

Methyl 3,3-dimethyl-4-oxobutanoate (10g, 70mmol), prepared according to the procedure of Hudlicky *et al.*, Synth. Commun., 16 169 (1986), was dissolved in 40mL of benzene, followed by addition of ethylene glycol (20mL), and *p*-toluenesulfonic acid monohydrate (1.3g). The reaction was refluxed with azeotropic removal of water for 1 hour. The reaction was poured into 200mL of ether, washed with saturated sodium bicarbonate, water and brine, dried with anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure to give 12.4g (94%) of the title compound.

Example 507B

trans, trans-2-(2,2,-Dimethyl-2-(1,3-dioxolan-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 502 and substituting methyl 3,3-dimethyl-3-(1,3-dioxolan-2-yl)propanoate for ethyl 3-methylhexanoate afforded the title compound, which was isolated by lyophilization from dilute aqueous TFA/CH_3CN. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.82-1.00 (m, 12H), 1.24-1.40 (m, 4H), 1.43-1.64 (m, 5H), 1.76-1.84 (m, 1H), 2.93-3.00 (m, 1H), 3.15-3.47 (m, 6H), 3.60-3.70 (m, 3H), 3.74-3.95 (m, 5H), 4.48 (s, 1H), 5.94 (m, 2H), 6.72 (d, J=8.0 Hz, 1H), 6.83 (dd, J=8.0, 1.2 Hz, 1H), 6.94 (d, J=1.2 Hz, 1H). MS (DCI/NH_3) m/e 533 $(M+H)^+$. Anal calcd for $C_{29}H_{44}N_2O_7$ • 1.1 TFA• 0.2 H_2O: C, 56.63; H, 6.93; N, 4.23. Found: C, 56.60; H, 6.96; N, 4.25.

Example 508

trans,trans-2-(2-(1,3-Dioxo-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[[*N*-4-heptyl-*N*-(2-methyl-3-fluorophenyl)] amino carbonylmethyl]-pyrrolidine-3-carboxylic acid

Example 508A

4-Heptanol

To an ice cooled solution of 1.14g (10.0 mmol) of 4-heptanone in 20 mL of diethyl ether was added 370 mg (10.0 mmol) of $LiAlH_4$, in portions to keep ether reflux at a minimum. After 45 minutes, the reaction was quenched by sequential dropwise addition of 0.4 mL H_2O, 0.4 mL 15% (*w/v*) NaOH(*aq*), and 1.2 mL H_2O. After stirring another 45 minutes, $MgSO_4$ was added until the salts were free flowing, then the reaction was filtered. The salts were washed with diethyl ether (3 x 5 mL), then the filtrate and washings were concentrated to a colorless oil. Yield 1.16g (100%).

Example 508B

4-Methanesulfonyloxyheptane

To an ice cooled solution of 834 mg (7.19 mmol) of 4-heptanol in 35 mL of CH_2Cl_2 was added 1.5 mL of triethylamine. Next, 0.7 mL (9 mmol) of

methanesulfonyl chloride was added, dropwise, over 1 minute. The mixture was stirred at 0 °C for 30 minutes, then extracted with H_20 (1 x 15 mL), 5% NH_4OH (2 x 15 mL), 1M HCl (2 x 15 mL), and brine (1 x 15 mL), dried over $MgSO_4$, filtered, and concentrated to an oil. Yield 1.31g (94%). ^1H NMR (300 MHz, $CDCl_3$) d 0.96 (t, 6, *J* = 9), 1.43 (m, 4), 1.64 (m, 4), 3.00 (s, 3), 4.73 (quintet, 1 *J* = 5).

Example 508C
4-Fluoro-3-methylaniline

To a solution of 20g (129 mmol) of 2-fluoro-5-nitrotoluene in 400 mL of ethanol was added 2g of 10% Pd-C. The mixture was shaken under 45 P.S.I. H_2 until hydrogen uptake ceased. The catalyst was filtered away and washed with ethanol, then the combined filtrate and washings were concentrated to 15.2 g (94%) of a colorless oil.

Example 508D
N-Heptyl-4-fluoro-3-methylaniline

To a solution of 4.10 g (3.28 mmol) of 4-fluoro-3-methylaniline in 30 mL of acetonitrile was added 7.64 g (3.93 mmol) of 4-methanesulfonyloxyheptane, and 3.4 g (4.1 mmol) of $NaHCO_3$(*s*). The mixture was stirred at reflux for 24 hours, then poured into 150 mL of H_2O and extracted with diethyl ether (2 x 30 mL). The combined ether layers were back extracted with brine (1 x 30 mL), dried over $MgSO_4$, filtered, and concentrated to an oil. This was purified via silica gel chromatography, eluting with 97.5: 2.5 hexanes: ethyl acetate, to give 2.56g (35%) of a pale yellow oil.

Example 508E
N,N-(4-Heptyl)-(4-fluoro-3-methyl)phenylbromoacetamide

To an ice cooled solution of 4.88g (21.9 mmol) of N-(4-heptyl)-4-fluoro-3-methylaniline and 4.9 mL (61 mmol) of pyridine in 100 mL of toluene was added a solution of 4.90 mL (56.2 mmol) of bromoacetyl bromide in 7 mL of toluene. The solution was stirred for 24 hours, gradually warming to 25 °C, then extracted with 1M HCl (1 x 100 mL). The aqueous layer was back extracted with diethyl ether (1 x 50 mL), then the combined organic layers were washed with H_2O (2 x 50 mL),

saturated $NaHCO_3(aq)$ (2 x 50 mL), and brine (1 x 50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to an oil. This was purified via silica gel chromatography, eluting with 90:10 hexanes: ethyl acetate to give 7.48g (99%) of a light yellow oil. ^1H NMR (300 MHz, $CDCl_3$) d 0.94 (t, 6, *J* = 5), 1.33 (m, 4), 1.43 (m, 4), 2.30 (s, 1.5), 2.31 (s, 1.5), 3.54 (s, 2), 4.72 (quintet, 1, *J* = 5), 6.96-7.04 (m, 2), 7.07(d, 1, *J* = 7).

Example 508F

trans,trans-2-(2-(1,3-Dioxol-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[[*N*-4-heptyl-*N*-(2-methyl-3-fluorophenyl)] amino carbonylmethyl]-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 502, substituting ethyl 5-(1,3-dioxolyl)-2-oxopentanoate for ethyl 3-methylhexanoate and *N,N*-(4-heptyl)-(4-fluoro-3-methyl)phenyl-bromoacetamide for *N,N*-dibutylbromoacetamide afforded the title compound as an amorphous solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.93 (brt, 6H), 1.23-1.47 (m, 8H), 1.67-2.10 (m, 4H), 2.32 (s, 3H), 3.16 (t, J = 9.0 Hz, 1H), 3.52-3.67 (brm, 2H), 3.73 (t, J = 9.0 Hz, 1H), 3.81-4.02 (m, 6H), 4.13 (brm, 1H), 4.72 (quintet, J = 6.9 Hz, 1H), 4.86 (t, J = 4.0 Hz, 1H), 5.93 (s, 2H), 6.72 (d, J = 8.1 Hz, 1H), 6.78 (dd, J = 1.8 Hz, 8.1 Hz, 1H), 6.85 (d, J = 1.8 Hz, 1H), 6.96 (m, 2H), 7.08 (t, J = 9.0 Hz, 1H). MS (DCI/NH_3) $(M+H)^+$ at m/e 599. Anal Calcd for $C_{33}H_{43}N_2O_7F \cdot 0.8$ TFA: C, 60.24; H, 6.40; N, 4.06. Found: C, 60.21; H, 6.14; N, 3.86.

Example 509

trans,trans-2-(2-(1,3-Dioxol-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 502, substituting ethyl 5-(1,3-dioxolyl)-2-oxopentanoate for ethyl 3-methylhexanoate and 6-methoxypiperonal for piperonal afforded the title compound as an amorphous solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, J = 7.8 Hz, 3H), 0.95 (t, J = 7.8 Hz, 3H), 1.31 (m, 4H), 1.53 (m, 4H), 1.90 (m, 2H), 2.09 (m, 2H), 3.19 (dd, J = 8.4 Hz, 8.4 Hz, 2H), 3.30 (q, J = 9.6 Hz, 2H), 3.25-3.42 (m, 1H), 3.73 (q, J = 10.5 Hz, 1H), 3.78-3.94 (m, 4H), 3.88 (s, 3H), 3.96 (dd, J = 5.1 Hz, 6.0 Hz, 1H), 4.03 (dd, J = 3.0 Hz, 6.3 Hz, 2H), 4.33 (m, 3H), 4.87 (t, J = 3.6 Hz, 1H), 5.94 (s, 2H), 6.53 (d, J = 1.8 Hz, 1H), 6.63 (d, J = 1.8 Hz, 1H). MS

(DCI/NH_3) $(M+H)^+$ at m/e 535. Anal calcd for $C_{28}H_{42}N_2O_8 \cdot 1.05$ TFA: C, 55.25; H, 6.63; N, 4.28. Found: C, 55.39; H, 6.66; N, 4.26.

Example 510

trans,trans-2-((2-Methoxyphenoxy)-methyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 502, substituting o-methoxyphenoxyacetic acid for 3-methylhexanoic acid, the above compound was prepared as an amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, J=7Hz, 3H), 0.90 (t, J=7Hz, 3H), 1.15-1.35 (m, 4H), 1.40-1.55 (m, 4H), 3.05-3.25 (m, 4H), 3.28-3.55 (m, 4H), 3.58-3.68 (m, 1H), 3.75-3.80 (m, 1H), 3.82 (s, 3H), 3.91 (d, J=14Hz, 1H), 4.05-4.15 (m, 1H), 4.23-4.33 (m, 1H),5.91 (s, 2H), 6.70 (d, J=8Hz, 1H), 6.82-6.95 (m, 5H), 7.03 (s, 1H). MS (DCI/NH_3) $(M+H)^+$ at m/e 541. Anal calcd for $C_{30}H_{40}N_2O_7$: C, 66.65; H, 7.46; N, 5.18. Found: C, 66.37; H, 7.61; N, 5.09.

Example 511

(2S,3R,4S)-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 511A

trans, trans-N-*tert*-Butoxycarbonyl-2-(2,2-dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylic acid

Ethyl *trans, trans*-2-(2,2-dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate (2.5g, 6.9mmol), prepared according to Example 503, was dissolved in 50mL of methylene chloride and di-*tert*-butyldicarbonate (1.5g) was added. After stirring overnight at room temperature, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with 10% ethyl acetate/hexanes to give the ethyl ester of the title compound (2.8g) as a colorless oil. The ester was dissolved in 50mL of ethanol followed by addition of sodium hydroxide (10mL of a 5M aqueous solution). After stirring for 20 hours at room temperature, the solvent was removed under reduced pressure, and the residue was dissolved in 150mL of water, and acidified with concentrated phosphoric acid. The mixture was extracted with chloroform (3X50mL), and the organic layers

were washed wiith brine, dried over anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure to give the title compound (2.4g) as a white foam.

Example 511B

Methyl *trans, trans*-2-(2,2-dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylate: As a single enantiomer

The product from Example 510A (1.97g, 4.5 mmol) was dissolved in 20mL of THF and cooled to 0°C, followed by addition of DMF (0.017mL, 5%), and oxalyl chloride (0.437mL, 5.00mmol). After 1 hour, solvent was removed at 0°C under a stream of nitrogen. The residue was dissolved in 5mL of benzene and evaporated. In a separate flask, (S)-4-benzyl-2-oxazolidinone (1.2g, 6.8mmol) was dissolved in 30mL of THF followed by addition of n-butyllithium (4.0mL of a 1.6M solution in hexanes) at 0°C, and the slurry was stirred for 15min. The acid chloride was dissolved in 20mL of THF and cooled to 0°C, followed by dropwise addition of the lithium oxazolide suspension via cannula. After 30min, the reaction was partitioned between ether and saturated bicarbonate. The organic phase was washed with water then brine, dried over anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with 15% ethyl acetate/hexanes to give the undesired diastereomer (1.17g, 43%), then elution with 20% ethyl acetate/hexanes gave the desired diastereomer (1.04g, 38%).

The desired diastereomer of the N-acyloxazolidinone (0.84g, 1.42mmol) was dissolved in 2.5mL of dichloromethane, and 2.5mL of trifluoroacetic acid was added. After 30min, the volatiles were removed under a stream of nitrogen, and the residue was twice dissolved in 5mL of toluene and evaporated under reduced pressure.

The TFA salt was stirred with 4mL of acetonitrile followed by addition of diisopropylethyl amine (1.0mL, 5.7mmol), and N-4-heptyl-N-(4-fluoro-3-methylphenyl)bromoacetamide (589mg, 1.7mmol) as a solution in 2mL of acetonitrile. After 21 hours, the reaction was warmed to 50°C for 3.5 hours. The reaction was cooled, the solvent removed under reduced pressure, and the residue was purified by flash chromatography on silica gel eluting with 20-30% ethyl acetate/hexanes to give 0.939g of amide as a colorless oil.

The above amide (200mg, 0.26mmol) was dissolved in 2.0mL of THF and 0.7mL of water. Solid lithium hydroxide monohydrate (22mg, 0.53mmol) was added at 0°C, followed by 30% hydrogen peroxide (0.050mL, 0.55mmol). After 1 hour, the reaction was warmed to room temperature. After an additional hour, the reaction was partitioned between 1:1 ethyl acetate:hexanes and water, 0.15g of sodium thiosulfate was added and the mixture was mixed thoroughly. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The crude residue was dissolved in 2mL of ether, and 1mL of methanol. A solution of (trimethylsilyl)diazomethane in hexanes was added dropwise until the yellow color remained. The reaction was quenched by addition of 2 drops of glacial acetic acid, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on 10g of silica gel eluting with 15-20% ethyl acetate/hexanes to give 70mg of the title compound as a crystalline solid (mp137.5°C).

Example 511C

(2S,3R,4S)-trans, trans-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylate

The product from Example 510B (65mg, 0.10mmol) was dissolved in 1.0mL of methanol and sodium hydroxide (0.1mL of a 5M aqueous solution) was added. After 2 hours, the reaction was warmed to reflux. After 6 hours, the reaction was cooled, and the solvent was removed under reduced pressure. The residue was dissolved in water and acidified with concentrated phosphoric acid. The aqueous solution was washed with chloroform (3X5mL), which was then washed with brine, dried with anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The title compound was isolated by lyophilization from dilute aqueous TFA/CH_3CN. ^1H NMR ($CDCl_3$, 300 MHz) d 0.78-0.95 (m, 15H), 1.04-1.46 (m, 12H), 1.76-2.95 (m, 2H), 2.31 (s, 3H), 3.23-3.33 (m, 1H), 3.47-3.58 (m, 1H), 3.6-3.75 (m, 2H), 3.80-3.95 (m, 2H), 4.05-4.15 (m, 1H), 4.73 (m, 1H), 5.94 (s, 2H), 6.70-6.80 (m, 2H), 6.82-6.93 (m, 2H), 6.96-7.14 (m, 2H). MS (DCI/NH_3) m/e 597 $(M+H)^+$. Anal calcd for $C_{35}H_{49}N_2FO_5 \cdot 0.05H_2O \cdot 0.8TFA$: C, 63.81; H, 7.30; N, 4.07. Found: C, 63.84; H, 7.18; N, 3.94. $[a]_D^{21}$ =+46° (c 2.7g/L, $CHCl_3$)

Example 512

trans,trans-2-(2-(2-Oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 512A

2-Oxopyrrolidin-1-ylpropionic acid

To a stirred solution of 5.0 mL (40.5 mmol) 2-oxopyrrolidin-1-ylpropionitrile in 15 mL of dioxane was added 8.1 mL of hydrochloric acid, a 6.0 M aqueous solution. The resulting mixture was then refluxed at 110 °C over night. The reaction mixture was then allowed to cool to room temperature, extracted with methylene chloride three times. The extracts were combined and washed with saturated brine solution once, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to give 1.60 g (25%) of acid as a brown oil.

Example 512B

Ethyl 5-(2-oxopyrrolidin-1-yl)-3-oxopentanoate

The title compound was prepared from the above acid by adapting the method of Bram and Vilkas, Bul. Chem. Soc. Fr., 945 (1964).

Example 512C

trans,trans-2-(2-(2-Oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 502, substituting ethyl 5-(2-oxopyrrolidin-1-yl)-3-oxopentanoate for ethyl 3-methylhexanoate afforded the title compound as an amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, J = 7.5 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H), 1.23-1.38 (m, 4H), 1.44-1.60 (m ,4H), 2.05 (t, J = 6.9 Hz, 2H), 2.12-2.25 (m, 1H), 2.38 (td, J = 4.2 Hz, 8.4 Hz, 2H), 2.47-2.61 (m, 1H), 3.17 (dd, J = 6.0 Hz, 8.7 Hz, 2H), 3.24 (t, J = 9 Hz, 1H), 3.32 (t, J = 7.8 Hz, 2H), 3.38-3.48 (m, 3H), 3.52 (t, J = 9 Hz, 1H), 3.66 (t, J = 6.9 Hz, 1H), 3.96 (m, 2H), 4.14 (m, 1H), 4.38 (brs, 2H), 5.93 (s, 2H), 6.74 (d, J = 8.1 Hz, 1H), 6.89 (dd, J = 1.8 Hz, 8.1 Hz, 1H), 6.87 (d, J = 1.8 Hz, 1H). MS (DCI/NH_3) $(M+H)^+$ at m/e 516. Anal calcd for $C_{28}H_{41}N_3O_6$·1.4 TFA: C, 54.78; H, 6.33; N, 6.22. Found: C, 54.69; H, 6.33; N, 6.14.

Example 513

<u>*trans,trans*-2-(2-(1,3-Dioxol-2-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid</u>

Using the procedures described in Example 502, substituting ethyl 5-(1,3-dioxolyl)-2-oxopentanoate for ethyl 3-methylhexanoate, N-4-heptyl-N-(4-fluoro-3-methylphenyl) bromoacetamide for N,N-dibutyl bromoacetamide and 6-methoxypiperonal for piperonal afforded the title compound as an amorphous solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.93 (br t, 6H), 1.23-1.47 (m, 8H), 1.67-2.10 (m, 4H), 2.32 (s, 3H), 3.16 (t, J = 9 Hz, 1H), 3.60-4.03 (m, 8H), 3.88 (s, 3H), 4.21 (brs, 1H), 4.72 (quintet, J = 6.6 Hz, 1H), 4.86 (t, J = 3.6 Hz, 1H), 5.93 (s, 2H), 6.49 (s, 1H), 6.61 (s, 1H), 6.96 (m, 2H), 7.08 (t, J = 9 Hz, 1H). MS (DCI/NH_3) $(M+H)^+$ at m/e 629. Anal calcd for $C_{34}H_{45}N_2O_8F \cdot 1.0$ TFA: C, 58.21; H, 6.24; N, 3.77. Found: C, 58.11; H, 6.11; N, 3.58.

<u>Example 514</u>

<u>*trans,trans*-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid</u>

Using the procedures described in Example 502, substituting ethyl 5-methyl-3-oxooctanoate for ethyl 3-methylhexanoate and 6-methoxypiperonal for piperonal afforded the title compound as an amorphous solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.81 (s, 3H), 0.84 (s, 3H), 0.86 (t, J = 6.9 Hz, 3H), 0.93 (t, J = 6.9 Hz, 3H), 0.96 (t, J = 6.9 Hz, 3H), 1.09-1.38 (m, 8H), 1.45-1.59 (m, 4H), 1.84-2.00 (m, 2H), 3.15 (dd, J = 6.9 Hz, 10.0 Hz, 2H), 3.30-3.42 (m, 3H), 3.72 (t, J = 10.5 Hz, 1H), 3.86 (t, J = 10.5 Hz, 1H), 3.88 (s, 3H), 4.02 (q, J = 10.0 Hz, 1H), 4.12 (d, J = 16.8 Hz, 1H), 4.29 (d, J = 16.8 Hz, 1H), 4.41 (brm, 1H), 5.94 (s, 1H), 6.52 (d, J = 1.8 Hz, 1H), 6.67 (d, J = 1.8 Hz, 1H). MS (DCI/NH_3) $(M+H)^+$ at m/e 533. Anal calcd for $C_{30}H_{48}N_2O_6 \cdot 0.9$ TFA: C, 60.12; H, 7.76; N, 4.41. Found: C, 60.18; H, 7.62; N, 4.33.

<u>Example 515</u>

<u>*trans,trans*-2-(2,2-dimethylpentyl)-4-(2,3-dihydro-benzofuran-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid</u>

Using the procedures described in Example 502, substituting ethyl 3,3-dimethylhexanoate for ethyl 3-methylhexanoate and 2,3-dihydro-benzofuran-5-

carbaldehyde for piperonal afforded the title compound as an amorphous solid by lyophylization with $CH_3CN/TFA/H_2O$. ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (s, 3H), 0.85 (s, 3H), 0.86 (t, J=7.2 Hz, 3H), 0.92 (t, J=7.2 Hz, 3H), 0.95 (t, J=7.2 Hz, 3H), 1.09-1.39 (m, 8H), 1.44-1.59 (m, 4H), 1.88 (dd, J=15.0, 7.2 Hz, 1H), 2.00 (d, J=15.0 Hz, 1H), 3.09 (m, 2H), 3.18 (t, J=9.0 Hz, 2H), 3.27-3.38 (m, 3H), 3.65-3.95 (m, 2H), 4.05 (q, J=10.0 Hz, 1H), 4.18 (d, J=16.8 Hz, 1H), 4.30-4.45 (m, 2H), 4.55 (t, J=9.0 Hz, 2H), 6.70 (d, J=8.4 Hz, 1H), 7.04 (dd, J=8.4, 2.1 Hz, 1H), 7.23 (brs, 1H). MS (DCI/NH_3) at m/e 501 $(M+H)^+$. Anal calc'd for $C_{30}H_{48}N_2O_4 \cdot 1.05$ TFA: C, 62.14; H, 7.97; N, 4.51. Found: C, 62.19; H, 8.00; N, 4.43.

Example 516

trans,trans-2-(2,2,-Dimethyl-2-(1,3-dioxolan-2-yl)ethyl)-4-(1-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 502, substituting methyl 3,3-dimethyl-3-(1,3-dioxolan-2-yl)propanoate for ethyl 3-methylhexanoate and 6-methoxypiperonal for piperonal afforded the title compound as an amorphous solid by lyophylization with $CH_3CN/TFA/H_2O$. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, J=7.2 Hz, 3H), 0.94 (t, J=7.2 Hz, 3H), 0.95 (s, 3H), 0.96 (s, 3H), 1.31 (sextet, J=7.2 Hz, 4H), 1.45 (m, 4H), 1.93 (dd, J=15.9, 6.0 Hz, 1H), 2.13 (d, J=15.9 Hz, 1H), 3.20 (dd, J=7.7, 7.7 Hz, 1H), 3.26-3.40 (m, 3H), 3.60 (m, 1H), 3.75-3.86 (m, 3H), 3.88 (s, 3H), 3.93-4.01 (m, 3H), 4.00-4.11 (m, 1H), 4.23 (d, J=15.9 Hz, 1H), 4.37-4.48 (m, 2H), 4.49 (s, 1H), 5.94 (s, 2H), 6.51 (d, J=2.1 Hz, 1H), 6.64 (d, J=2.1 Hz, 1H). MS (DCI/NH_3) at m/e 563 $(M+H)^+$. Anal calcd for $C_{30}H_{46}N_2O_8 \cdot 0.9$ TFA: C, 57.41; H, 7.11; N, 4.21; found: C, 57.35; H, 6.86; N, 4.05.

Example 517

trans,trans-2-(2-(2-Methoxyphenyl)-ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 502, substituting o-methoxyphenylpropionic acid for 3-methylhexanoic acid, the above compound was prepared as an amorphous solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, J=7Hz, 3H), 0.91 (t, J=7Hz, 3H), 1.10-1.27 (m, 4H), 1.42-1.60 (m, 4H), 1.72-1.89 (m, 1H), 1.91-

2.02 (m, 1H), 2.55-2.77 (m, 2H), 2.94 (t, J=6Hz, 1H), 3.05-330 (m, 6H), 3.59-3.82 (m, 3H), 3.73 (d, J=14Hz, 1H), 3.77 (s, 3H), 5.91 (s, 2H), 6.70 (d, J=8Hz, 1H), 6.78-6.88 (m, 3H),6.92 (d, J=2Hz, 1H), 7.08-7.19 (m, 2H). MS (DCI/NH_3) $(M+H)^+$ at m/e 539. Anal calcd for $C_{31}H_{42}N_2O_6$: C, 69.12; H, 7.86; N, 5.20. Found: C, 68.89; H, 7.70; N, 4.99.

Example 518

trans, trans-2-(2,2-Dimethyl-3-(*E*)-pentenyl)-4-(1-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 518A

4-Methyl-3-penten-2-ol

To a stirred solution of 3-methyl-2-butenal (8.7g, 103mmol) in 100mL of tetrahydrofuran under N_2 at 0 °C was added methylmagnesium bromide (38mL of a 3.0M solution in ethyl ether, 114mmol) dropwise. The resulting mixture was allowed to warm to room temperature slowly and stirred at room temperature for 1 hour before it was quenched with 25mL of saturated NH_4Cl. The resulting biphasic mixture was partitioned between ethyl ether and water. The organic layer was washed with brine, dried with anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure to give 8.4g (81%) of alcohol as a colorless oil.

Example 518B

trans-Ethyl 3,3-dimethyl-4-pentenoate

A mixture of 4-methyl-3-penten-2-ol (7.4g, 74mmol), triethyl orthoacetate (13.6mL, 74mmol) and propionic acid (0.28mL, 3.7mmol) was heated at 150 °C for 7 hours. The product was then distilled under normal pressure (200-220 °C) to give 5.0g of crude ester as a colorless oil.

Example 518C

trans, trans-2-(2,2-Dimethyl-3-(*E*)-pentenyl)-4-(1-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 502, substituting *trans*-ethyl 3,3-dimethyl-4-pentenoate for ethyl 3-methylhexanoate and 6-methoxypiperonal for piperonal afforded the title compound as an amorphous solid by lyophilization from dilute aqueous TFA/CH_3CN. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, J=7.2 Hz, 3H), 0.95 (t, J=7.2 Hz, 3H), 0.97 (s, 3H), 0.99 (s, 3H), 1.31 (sextet, J=7.2 Hz, 4H), 1.52 (quintet, J=7.2 Hz, 4H), 1.58 (d, J=5.4 Hz, 3H), 1.92 (dd, J=15.0, 6.6 Hz, 1H), 2.04 (d, J=15.0 Hz, 1H), 3.15 (dd, J=7.8, 7.8 Hz, 1H), 3.30-3.40 (m, 3H), 3.75 (m, 2H), 3.87 (s, 3H), 3.99 (q, J=9 Hz, 2H), 4.11-4.30 (m, 3H), 5.29 (d, J=15.6 Hz, 1H), 5.38 (dd, J=15.6, 6 Hz, 1H), 5.94 (s, 2H), 6.50 (d, J=1.8 Hz, 1H), 6.63 (d, J=1.8 Hz, 1H). MS (DCI/NH_3) at m/e 531 $(M+H)^+$. Analysis calc'd for $C_{30}H_{46}N_2O_6 \cdot 0.95$ TFA: C, 59.95; H, 7.41; N, 4.38; found: C, 60.00; H, 7.33; N, 4.35.

Example 519

trans, trans-2-(3-(2-pyridyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 519A

3-(2-Pyridyl)-propionic Acid

In a 50 mL round-bottomed flask equipped with a stirring bar was placed 3-(2-pyridyl)-propanol (1 g, 7.6 mmol), water (13 mL) and concentrated sulfuric acid (0.5 g, 5.1 mmol). To this stirred solution was added over a period of 30 min potassium permanganate (1.8 g, 11.3 mmol) while the reaction temperature was maintained at 50 °C. After the addition was completed, the mixture was held at 50 °C until the color of the reaction mixture turned brown, then heated at 80 °C for 1 hour and filtered. The filtrate was evaporated to dryness to yield quantitatively the desired acid (1.14 g) suitable for next step without further purification. To prepare a pure acid, the residue thus obtained was boiled in ethanol (10 mL) in the presence of charcoal (0.1 g) for 5 min, filtered and cooled to give crystalline 3- (2-pyridyl)-propionic acid (0.88 g, 78%).

Example 519B

trans, trans-2-(3-(2-pyridyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedure described in Example 502, the title compound was isolated by lyophilization from dilute aqueous TFA/CH_3CN as an amorphous solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.65 (d, J=6.0 Hz, 1H), 8.06 (t, J=6.91 Hz, 1H), 7.70 (d, J=9.0 Hz, 1H), 7.51 (t, J=6.91 Hz, 1H), 6.82-6.66 (m, 3H), 5.91 (s, 2H), 4.45 (s, 2H), 4.29-4.18 (m, 1H), 4.04 (dd, J=20.1, 10.5 Hz, 1 H), 3.84 (t, J=12.6 Hz, 1 H), 3.62 (dd, J=13.8, 9.6 Hz, 1H), 3.46-3.13 (m, 7H), 2.51 (broad s, 2H), 1.60-1.43 (m, 4H), 1.37-1.22 (m, 4H), 0.91 (t, J=8.4 Hz, 6H). MS (DCI/NH_3) m/e 510 $(M+H)^+$. Anal calcd for $C_{29}H_{39}N_3O_5$• 1.75 TFA: C, 55.04; H, 5.79; N, 5.92. Found: C, 55.08; H, 5.64; N, 5.81.

Example 520

(2S, 3R, 4S)-2-(2-(2-oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 520A

(2S, 3R, 4S)-Ethyl-2-(2-(2-oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylate-(S)-Mandelate

The racemic amino ester from Example 512 (3.45g, 8.98mmol) in 10mL of ethyl acetate was treated with (*S*)-(+)-mandelic acid (0.75g, 4.93mmol). Upon the formation of the clear solution, hexane was dropped in slowly with stirring till the solution became light cloudy. The solution was left stirred at room temperature over night. The crystals was then collected by filtration, recrystalized from ethyl acetate/hexane twice to give a yield of 800 mg (17%) of pure salt.

Example 520B

(2S, 3R, 4S)-Ethyl-2-(2-(2-oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylate

To a stirred solution of pure mandelate (150 mg, 0.28 mmol) in CH_3CN was added *N,N*-dibutylbromoacetamide(84 mg, 0.34 mmol) and diisopropylethylamine (98uL, 0.56mmol). The resulting mixture was stirred at room temperature over night. Solvent was then removed under reduced pressure and the crude product was purified by silica gel flash chromatography to give 140 mg (90% yield) of the title compound.

Example 520C

(2S, 3R, 4S)-2-(2-(2-oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 502, the title compound was prepared as an amorphous solid by lyophylization with $CH_3CN/TFA/H_2O$. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, J = 7.5 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H), 1.23-1.38 (m, 4H), 1.44-1.60 (m ,4H), 2.05 (t, J = 6.9 Hz, 2H), 2.12-2.25 (m, 1H), 2.38 (td, J = 4.2 Hz, 8.4 Hz, 2H), 2.47-2.61 (m, 1H), 3.17 (dd, J = 6.0 Hz, 8.7 Hz, 2H), 3.24 (t, J = 9 Hz, 1H), 3.32 (t, J = 7.8 Hz, 2H), 3.38-3.48 (m, 3H), 3.52 (t, J = 9 Hz, 1H), 3.66 (t, J = 6.9 Hz, 1H), 3.96 (m, 2H), 4.14 (m, 1H), 4.38 (brs, 2H), 5.93 (s, 2H), 6.74 (d, J = 8.1 Hz, 1H), 6.89 (dd, J = 1.8 Hz, 8.1 Hz, 1H), 6.87 (d, J = 1.8 Hz, 1H). MS (DCI/NH_3) $(M+H)^+$ at m/e 516. Anal calcd for $C_{28}H_{41}N_3O_6 \cdot 0.85$ TFA: C, 58.23; H, 6.89; N, 6.86. Found: C, 58.37; H, 6.90; N, 6.84.

Example 521

(2S, 3R, 4S)-2-(2-(2-oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 520, substituting *N,N*-(4-heptyl)-(4-fluoro-3-methyl)phenyl-bromoacetamide for *N,N*-dibutylbromoacetamide afforded the title compound as an amorphous solid by lyophylization with $CH_3CN/TFA/H_2O$. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85-0.98 (m, 6H), 1.22-1.55 (m, 8H), 2.04 (quintet, J=7.9 Hz, 4H), 2.32 (s, 3H), 2.36 (t, J=7.9 Hz, 2H), 2.61 (m, 1H), 3.14 (m, 1H), 3.25-3.61 (m, 5H), 3.66-3.77 (m, 1H), 3.79-3.90 (m, 2H), 3.92-4.03 (m, 1H), 4.69 (quintet, J=6.8 Hz, 1H), 5.95 (s, 2H), 6.71 (s, 2H), 6.78 (s, 1H), 6.93-7.13 (m, 3H); MS (DCI/NH_3) at m/e 610 $(M+H)^+$. Anal calc'd for $C_{34}H_{44}N_3O_6F_1 \cdot 1.45$ TFA: C, 57.18; H, 5.91; N, 5.42. Found: C, 57.20; H, 5.62; N, 5.52.

Example 522

trans, trans-2-(2-(1-pyrazolyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 522A

3-(1-Pyrazolyl)-propionic Acid

In a 10 mL round-bottomed flask equipped with a condenser and a stirring bar was placed pyrazole (0.50 g, 7.3 mmol), acrylic acid (0.50 mL, 7.3 mmol) and triethylamine (3 mL). The reaction mixture was refluxed for 6 hours. After removing triethylamine, the viscous oil was dried on high vacuo during 12 hours to yield quantitatively the desired acid (1.0 g) suitable for the next step without further purification.

Example 522B

trans, trans-2-(2-(1-pyrazolyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedure described in Example 502, the title compound was isolated by lyophilization from dilute aqueous TFA/CH_3CN as an amorphous solid ^1H NMR ($CDCl_3$, 300 MHz) δ 7.56 (d, J=3.0 Hz, 1H), 7.50 (d, J=3 Hz, 1H), 6.83-6.66 (m, 3H), 6.28 (t, J=3 Hz, 1H), 5.91 (s, 2H), 4.55-3.98 (m, 6H), 3.83-3.72 (t, J=10.5 Hz, 1H), 3.61-3.40 (t, J=10.5 Hz, 1 H), 3.36-3.12 (m, 5H), 2.69-2.43 (m, 2H), 1.59-1.42 (m, 4H), 1.38-1.21 (m, 4H), 0.91 (t, J=7.5 Hz, 6H). MS (DCI/NH_3) at m/e 499 $(M+H)^+$. Anal calcd for $C_{27}H_{38}N_4O_5 \cdot 0.75$ TFA: C, 58.60; H, 6.69; N, 9.59. Found: C, 58.53; H, 6.45; N, 9.67.

Example 523

trans, trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(3-hydroxypropyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid

Example 523A

N-Butyl-N-(3-hydroxypropyl)-amine

To a solution of 15.9g (100 mmol) of methyl 3-*N*-(n-butyl)aminopropionate in 150 mL of diethyl ether at 0 C was added 50 mL (0.35 mmol) of 1.0M $LiAlH_4$ in diethyl ether, keeping reflux at a minimum. The mixture was stirred at 0 C for 2.25 hours, the quenched by sequential dropwise addition of 1.9 mL H_2O, 1.9 mL 15%w/v $NaOH_{(aq)}$, and 5.7 mL H_2O. After stirring for 30 min, the salts were filtered

and washed with diethyl ether, then the filtrate was concentrated to 11.3 g (86%) of a light yellow oil.

Example 523B

N-Butyl-N-(3-hydroxypropyl)-chloroacetamide

To an ice cooled solution of 1.31g (10.0 mmol) of *N*-butyl,*N*-(3-hydroxypropyl)amine in 20 mL of ethyl acetate was added a solution of 1.71g (10.0 mmol) of chloroacetic anhydride in 10mL of ethyl acetate. The mixture was stirred, and gradually warmed to room termperature over 18 hours. The reaction was extracted with H_2O (1 x 50 mL), saturated $NaHCO_3$ (*aq*) (2 x 50 mL), and brine (1 x 50 mL), dried over $MgSO_4$, filtered, and concentrated to an oil. The product was purified *via* silica gel chromatography, eluting with 80:20 hexanes:ethyl acetate to give 723 mg (35%) of a light yellow oil.

Example 523C

trans, trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(3-hydroxypropyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1D, substituting N-butyl-N-(3-hydroxypropyl)-chloroacetamide for N-propyl bromoacetamide and adding DMSO as cosolvent, afforded the title compound, which was isolated by lyophilization from dilute aqueous TFA/CH_3CN. ^1H NMR (CD_3OD, 300 MHz) δ 0.78-0.95 (m, 3H), 1.00-1.80 (m, 4H), 2.80-3.65 (m, 15H), 3.80 (d, J=1.5 Hz, 2H), 5.93 (s, 2H), 6.72-7.05 (m, 5H), 7.33-7.40 (m, 2H). MS (DCI/NH_3) at m/e 513 $(M+H)^+$. Anal calc'd for $C_{28}H_{36}N_2O_7 \cdot 1.6\ H_2O$: C, 62.12; H, 7.30; N, 5.17. Found: C, 62.04; H, 7.21; N, 4.88.

Example 524

trans, trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-propyl-N-propoxyamino)carbonylmethyl]-pyrrolidine-3-carboxylic acid

Example 524A

N-Boc-O-allylhydroxylamine

O-Allylhydroxylamine hydrochloride hydrate (5.0g) was dissolved in THF (15 mL). The solution was cooled to 0°C in an ice bath. Diisopropylethylamine (8mL) and di-t-butyldicarbonate (10.0g) were added. The mixture was stirred at 0°C for 1 hour at which point the bath was removed and the reaction allowed to warm to room temperature and stirred overnight. The THF was removed *in vacuo* and the residue taken up in EtOAc (25 mL), and washed with water (1 x 50 mL), saturated sodium bicarbonate solution (3 x 50 mL), 1N phosphoric acid (3 x 50 mL), and brine (1 x 50 mL). The organic layer was dried with sodium sulfate and evaporated to give a light yellow oil (6.5g) which was used without any further purification.

Example 524B

N-Boc-N-propyl-O-allylhydroxylamine

N-Boc-O-allylhydroxylamine (6.5g) from the above procedure was dissolved in dry THF (25 mL) and the solution cooled to 0°C in an ice bath. Sodium hydride (1.5g, 60% dispersion in oil) was added portionwise over 5 min. The resulting mixture was stirred for 30 min at 0°C. 1-Iodopropane (3.8mL) was added dropwise to the mixture. The reaction was stirred at 0°C for 1 hour, then stirred overnight at room temperature. The THF was removed *in vacuo* and the residue taken up in EtOAc (50 mL) and washed with water (1 x 50 mL), saturated sodium bicarbonate solution (3 x 50 mL), 1N phosphoric acid (3 x 50 mL), and brine (1 x 50 mL). The organic layer was dried with sodium sulfate and evaporated to give a light yellow oil, which was purified by flash chromatography on silica gel eluting with 5% EtOAc/hexanes to give the title compound as a colorless oil (6.0g).

Example 524C

N-Boc-N-propyl-N-propoxyamine

N-Boc-N-propyl-O-allylhydroxylamine (6.0g) was dissolved in EtOAc (100 mL). 10% Palladium-on-carbon (0.5g) was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at room temperature for 6 hours. The catalyst was removed by filtration through a pad of Celite and the solvents were removed *in vacuo* to give a yellow oil which was purified by flash chromatography on silica gel eluting with 5% EtOAc/hexanes to give the title compound as a colorless oil (5.8g).

Example 524D

N-Propyl-N-propoxyamine hydrochloride

N-Boc-N-propyl-N-propoxyamine (5.8g) was dissolved in 4N HCl/dioxane (10mL) and stirred at room temperature for 7 hours. The solvent was removed *in vacuo* and the residue triturated with diethyl ether. The resulting yellow solid (2.1g) was collected by filtration and washed with diethyl ether.

Example 524E

N-propyl-N-propoxy-bromoacetamide

N-Propyl-N-propoxyamine hydrochloride (0.30 g) was dissolved in acetonitrile and cooled to -20°C. Pyridine (0.2 mL) was added. Bromoacetyl bromide (0.15g) was added dropwise over 5 min. The solution was stirred at -20°C for 30 min. The bath was removed and the solution was stirred for 6 hours at room temperature. The solvent was removed *in vacuo* and the residue taken up in EtOAc (50 mL) and washed with water (1 x 25 mL), 1N phosphoric acid (3 x 25 mL), and brine (1 x 25 mL). The organic layer was dried with sodium sulfate and evaporated to give a dark orange oil (0.35g). The product is a mixture of chloro- and bromoacetamides in a ratio of ~3:1.

Example 524F

trans, trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(3-hydroxypropyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid

Prepared according to the procedure of Example 523C, employing N-propyl-N-propoxy-bromoacetamide and ethyl 2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate. The crude product was purified by preparative HPLC (Vydac mC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The appropriate fraction was lyophilized to give the product as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (m, 6H, J=8Hz), 1.49 (m, 2H, J=8Hz), 1.61 (m, 2H, J=8Hz), 3.55 (m, 6H), 3.80 (m, 2H), 3.81 (s, 3H), 4.00 (m, 2H), 4.13 (d, 2H, J=17Hz), 5.96 (s, 2H), 6.77 (d, 1H, J=9Hz), 6.90 (m, 3H), 7.05 (d, 1H, J=1Hz), 7.44 (d, 2H, J=9Hz). MS (DCI/NH_3) m/e 499 $(M+H)^+$. Anal calcd for $C_{27}H_{34}N_2O_7$. 1.20 TFA: C, 55.57; H, 5.58; N, 4.41. Found: C, 55.59; H, 5.58; N, 4.55.

Example 525

trans, trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-propoxyamino)carbonylmethyl]-pyrrolidine-3-carboxylic acid

Example 525A

N-butyl-N-(2-hydroxyethyl)-amine

In a thick walled glass tube 5 ml (100 mmol) of ethylene oxide was condensed at -78 C. To this12.5 ml (120 mmol) of butylamine was added and the tube was sealed. The resultant solution was allowed to heat in an oil bath at 50 C for 18 hours. Unreacted reagents were removed by evaporation to give the title compound.

Example 525B

N-Butyl-N-(2-azidoethyl)-chloroacetamide

To 500 mg of N-butyl,N-2-hydroxyethylamine was added 2 mL of thinoyl chloride, dropwise. After the initial reaction had ceased, the reaction was stirred for 10 min, then concentrated to an oil. Diethyl ether was added and evaporated to aid in removal of the thionyl chloride. The residue was taken up in 10 mL of DMF, and 1.0g (16 mmol) of sodium azide was added. The reaction was stirred at 75 C for 2 hours, then poured into 50 mL of 0.6M $NaHCO_3$(*aq.*) and extracted with diethyl ether (3 x 15 mL). The combined ether layers were back extracted with brine (1 x 15 mL), dried over $MgSO_4$, and filtered. To the ether solution was added 850 mg (4.97 mmol) of chloroacetic anhydride. The reaction was stirred for 10 min, then concentrated to an oil. This was taken up in 10 mL of saturated $NaHCO_3$(*aq.*) and extracted with diethyl ether (3 x 5 mL). The combined ether layers were back extracted with brine (1 x 5 mL), dried over $MgSO_4$, filtered, and concentrated to an oil. This was purified *via* silica gel chromatography, eluting with 30% ethyl acetate: hexanes, to give 161 mg (17%) of an oil.

Example 525C

trans, trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(2-aminoethyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid

According to the procedure of Example 523C, N-butyl-N-(2-azidoethyl)-chloroacetamide was coupled with ethyl 2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate. The crude product was chromatographed on silica, using 40% EtOAc in hexanes to elute. The product was dissolved in a solution of ethanol and aqueous 2.5 N sodium hydroxide and stirred for 3 hours at room temperature. The solution was concentrated *in vacuo* and water added. The mixture was extracted with ether; the aqueous layer was acidified to pH 4 with 1N H_3PO_4 and extracted with EtOAc. The latter organic extract was washed with brine and dried over Na_2SO_4. To 100 mg (0.10 mmol) of the azide was added 1mL of 1M $HCl_{(aq.)}$, 0.5 mL of dioxane, and 5 mg of 10% Pd-C. The suspension was stirred under 1 atm. of H_2 for 5 hours, then filtered and concentrated to a white solid. The product was purified via HPLC, eluting with a 0 to 70 CH_3CN in 0.1% aqueous TFA gradient to give the title compound as its TFA salt. ^1H NMR (CD_3OD, 300 MHz) δ 0.92 (t, J=7.0 Hz, 3H), 0.96 (t, rotamer), 1.23 (m, 2H), 1.41 (m, 2H), 3.06 (m, 4H), 3.39 (m, 2H), 3.69 (m, 2H), 3.84 (s, 3H), 3.94 (m, 3H), 4.18 (m, 2H), 5.05 (bd, J=10.7 Hz, 1H), 5.98 (s, 2H), 6.84 (d, J=7.7 Hz, 1H), 6.93 (dd, J=1.8, 8.1 Hz, 1H), 7.05 (m, 3H), 7.56 (m, 2H). MS (DCI/NH_3) at m/e 498 $(M+H)^+$. Anal calcd for $C_{27}H_{35}N_3O_6$• 3.15 TFA: C, 46.68. H, 4.49. N, 4.90. Found: C, 46.61; H, 4.73; N, 4.79.

Example 526

trans, trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(3-aminopropyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid

To and ice-cold solution of the compound of Example 523C (100 mg, 0.19 mmol) in 1 mL of dichloromethane was added 17mL of methanesulfonyl chloride, and 39 mL of triethylamine. The mixture was stirred for 20 min, then diluted with 1.5 mL of dichloromethane and extracted once with 5mL of water to which had been added 1 drop of 85% H_3PO_4, then 5% ammonium hydroxide (1 x 2.5 mL), and brine (1 x 2.5 mL), dried over $MgSO_4$, filtered, and concentrated to an oil. To a solution of 81 mg (0.13 mmol) of the mesylate in 1mL of DMF was added 65 mg (10 mmol) of sodium azide. The mixture was stirred for 1 hour at 50 C, then poured into 10 mL of water and extracted with diethyl ether (3 x 5 mL). The combined ether layers were back extracted with brine (1 x 5 mL), dried over $MgSO_4$, filtered, and concentrated to an oil. This was purified *via* silica gel chromatography, eluting with 60:40 hexanes:

ethyl acetate to give 57 mg of a colorless oil. The product was dissolved in a solution of ethanol and aqueous 2.5 N sodium hydroxide and stirred for 3 hours at room temperature. The solution was concentrated *in vacuo* and water added. The mixture was extracted with ether; the aqueous layer was acidified to pH 4 with 1N H_3PO_4 and extracted with EtOAc. The latter organic extract was washed with brine and dried over Na_2SO_4. To this azide was added 1mL of 1M HCl(*aq.*), 0.5 mL of dioxane, and 5 mg of 10% Pd-C. The suspension was stirred under 1 atm. of H_2 for 5 hours, then filtered and concentrated to a white solid. The product was purified via HPLC, eluting with a 0 to 70 CH_3CN in 0.1% aqueous TFA gradient to give the title compound as its TFA salt. ^1H NMR (D_6-DMSO, 300 MHz) δ 0.85 (apparent q, J=6.8 Hz, 3H), 1.17 (m, 2H), 1.30 (m, 2H), 1.67 (m, 2H), 2.71 (m, 2H), 3.04 (m, 1H), 3.21 (m, 3H), 3.45 (m, 1H), 3.75 (m, 3H), 3.97 (s, 3H), 3.85-4.80 (broad m, 3H), 6.03 (m, 2H), 6.87 (dd, J=1.4, 8.1 Hz, 1H), 6.92 (d, J=7.8 Hz, 1H), 7.01 (m, 2H), 7.16 (m, 1H), 7.55 (m, 2H), 7.72 (m, 2H), 7.85 (m, 1H); MS (DCI/NH_3) $(M+H)^+$ at m/e 512. Anal calcd for $C_{28}H_{37}N_3O_6$• 3.0 TFA: C, 47.84. H, 4.72. N, 4.92. Found: C, 47.86; H, 4.75; N, 4.97.

Example 527

trans, trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(3-dimethylaminopropyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid

Example 527A

N-butyl-N-(3-bromopropyl)bromoacetamide

To 1.50g (11.4 mmol) of N-butyl-N-(3-hydroxy)propylamine was added 3 mL of 48% HBr(*aq.*), and 1.5 mL of conc. H_2SO_4. The reaction was stirred at reflux for 3 hours, then cooled to room temperature and stirred for 22 hours. The mixture was poured over 50 mL of ice, and the solution was treated with 50 mL of 2M NaOH(*aq.*). The basic solution was extracted with ethyl acetate (3 x 25 mL), then the combined ethyl acetate layers were back extracted with brine (1 x 25 mL), dried, and filtered. To the ice cooled ethyl acetate solution was added 3mL of triethylamine, then 1.5 mL of bromoacetyl bromide as a solution in 3.5 mL of ethyl acetate. The reaction was stirred at 0 C for 30 min, then extracted with 1M HCl(*aq.*) (2 x 25 mL) saturated $NaHCO_3$(*aq.*) (1 x 25 mL) and brine (1 x 25 mL). The organic layer was dried over MgSO4, filtered, and concentrated to an oil. This was purified via silica gel

chromatography, eluting with 30% ethyl acetate in hexanes to give 1.47g of a colorless oil.

Example 527B

Ethyl *trans, trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(3-bromopropyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylate

According to the procedure of Example 523C, N-butyl-N-(3-bromopropyl-bromoacetamide was coupled with ethyl 2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate. The crude product was chromatographed on silica, using 40% EtOAc in hexanes to elute.

Example 527C

trans, trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(3-dimethylaminopropyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid

To 400 mg (0.663 mmol) of the compound of Example 527B in 4 mL of absolute EtOH was added 1.2 mL of 2.0 M Me_2NH in THF. The reaction was heated at 50 C for 3h, then stirred at room temperature for 18 hours. The mixture was concentrated, then reconcentrated from CH_3CN to remove most of the trimethylamine. The product was purified via silica gel chromatography, eluting with 9:1 CH_2Cl_2: MeOH over about 20 mL of silica gel to give the ethyl ester. The product was dissolved in a solution of ethanol and aqueous 2.5 N sodium hydroxide and stirred for 3 hours at room temperature. The solution was concentrated *in vacuo* and water added. The mixture was extracted with ether; the aqueous layer was acidified to pH 4 with 1N H_3PO_4, and the product was purified by preparative HPLC. ^1H NMR (CD_3OD, 300 MHz) δ 0.92 (t, J=7.0 Hz, 3H), 1.22 (m, 2H), 1.39 (m, 2H), 1.90 (m, 2H), 2.87 (s, 6H), 3.07 (m, 4H), 3.24 (m, 1H), 3.43 (m, 1H), 3.62 (m, 1H), 3.84 (s, 3H), 3.88 (m, 3H), 4.07 (m, 1H), 4.17 (m, 1H), 4.97 (m, 1H), 5.97 (s, 2H), 6.83 (d, J=8.1 Hz, 1H), 6.93 (dd, J=1.7, 8.1 Hz, 1H), 7.05 (m, 3H), 7.53 (m, 2H). MS (DCI/NH_3) at m/e 540 $(M+H)^+$. Anal calcd for $C_{30}H_{41}N_3O_6 \cdot 2.95$ TFA: C, 49.22. H, 5.06. N, 4.80. Found: C, 49.16; H, 5.11; N, 4.62.

Example 528

<u>*trans, trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(3-trimethylammoniopropyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid</u>

Prepared according to the procedures of Example 527C, substituting aqueous Me_3N for Me_2NH. ^1H NMR (CD_3OD, 300 MHz) δ 0.91 (m, 3H), 1.24 (m, 2H), 1.40 (m, 2H), 1.99 (m, 2H), 3.13 (s, 9H), 3.18 (s, rotamer), 3.20 (m, 3H), 3.39 (m, 4H), 3.72 (m, 1H), 3.84 (s, 3H), 4.03 (m, 3H), 4.35 (m, 1H), 5.19 (m, 1H), 5.97 (s, 2H), 6.84 (d, J=8.1 Hz, 1H), 6.96 (dd, J=1.7, 7.9 Hz, 1H), 7.10 (m, 3H), 7.62 (m, 2H). MS (DCI/NH_3) at m/e 554 $(M+H)^+$. Anal calcd for $C_{31}H_{44}N_3O_6 \cdot 0.1\ H_2O \cdot 1.65$ TFA: C, 47.25. H, 4.96. N, 4.32. Found: C, 47.25; H, 4.74; N, 4.75.

<u>Example 529</u>

<u>*trans, trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-aminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid</u>

<u>Example 529A</u>

<u>N-butyl-N-(4-hydroxybutyl)-amine</u>

A solution of 8.1 g (110 mmol) of *n*-butylamine and 8.6 g of butyrolactone in 50 ml toluene was allowed to reflux under nitrogen atmosphere for 50 hours. Volatile solvents were removed *in vacuo*. To a solution of 3.18 gm (20 mmol) of the resultant N-butyl -4-hydroxybutyramide in 50 ml of toluene were added 120 ml (120 mmol) DIBAL(25%W). The solution was heated with stirring at 70 C for 18 hours. After cooling to 0 C, the reaction was quenched with methanol (1/3 amount of DIBAL solution was used) followed by addition of saturated solution of Rochelle's salt. The mixture was extracted twice with EtOAc; the organic extracts were washed with brine and dried over Na_2SO_4.

<u>Example 529B</u>

<u>N-butyl-N-(4-hydroxybutyl)-chloroacetamide</u>

Pyridine (2 ml) was added to an ice cold solution of 0.58 gm (4 mmol) of N-butyl-N-(4-hydroxybutyl)-amine in 10 ml of EtOAc. To this solution 0.769 gm (4.5 mmol) chloroacetic anhydride was added in small portions. The reaction mixture was allowed to stir for 5 hours at 0 C, and then was allowed to warm to room

temperature. Bicarbonate was added, and the resultant mixture was extracted with EtOAc. The organic layer was washed with water and brine. The crude material was purified by column chromatography.

Example 529C

Ethyl *trans, trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-hydroxybutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylate

According to the procedure of Example 523C, N-butyl-N-(4-hydroxybutyl-chloroacetamide was coupled with ethyl 2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate. The crude product was chromatographed on silica gel.

Example 529D

Ethyl *trans, trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-bromobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylate

To the solution of 0.180 gm (0.33 mmol) of the compound of Example 529C in 2 ml DMF 0.086 gm (1 mmol) of lithium bromide and 0.120 ml (0.66 mmol) of PBr_3 was added. The reaction mixture was allowed to stir at 0 C for 2 hours and was slowly warmed to room temperature. Bicarbonate was added, and the resultant mixture was extracted with EtOAc. The organic layer was washed with water and brine. The crude material was purified by column chromatography.

Example 529E

trans, trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-aminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid

To a solution of 0.135 gm (0.21 mmol) of the compound of Example 529D in 2 ml DMF was added 0.1 gm of sodium azide. Reaction was allowed to stir at room temperature for 18 hours under nitrogen atmosphere. After addition of water, the product was extracted into EtOAc. The crude product (117 mg) was dissolved in 10 ml ethanol under nitrogen atmosphere. To this 45 mgs of 10% Pd/C catalyst was added, the nitrogen from the reaction flask was evacuated and was flushed with hydrogen by placing a balloon filled with hydrogen.
The reaction was allowed to stir for 4 hours under hydrogen atmosphere, and was worked up by filtering through a Celite pad. The product was dissolved in a solution

of ethanol and aqueous 2.5 N sodium hydroxide and stirred for 8 hours at room temperature. The solution was concentrated *in vacuo* and water added. The mixture was extracted with ether; the aqueous layer was acidified to pH 4 with 1N H_3PO_4, and the product was purified by preparative HPLC. ^1H NMR (CD_3OD, 300 MHz) δ 0.90 (t, J=7 Hz, 3H), 1.10-1.65 (m, 6H), 2.85-2.95 (m, 2H), 3.00-4.10 (m, 14H), 5.50 (d, J=3 Hz, 2H), 5.97 (s, 2H), 6.82 (d, J=8 Hz, 1H), 6.91 (dd, J=7 Hz, 1H), 7.00-7.06 (m, 3H), 7.45-7.55 (m, 2H). MS (DCI/NH_3) at m/e 526 $(M+H)^+$. Anal calc'd for $C_{29}H_{39}N_3O_6$.2.2 TFA: C, 51.75; H, 5.35; N, 5.41. Found: C, 51.75; H, 5.31; N, 5.30.

Example 530

trans, trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid

The title compound was prepared from the compound of Example 529D, employing the procedures of Example 527C. ^1H NMR (CD_3OD, 300 MHz) δ 0.90 (dt, J=7Hz, 3H), 1.1-1.75 (m, 8H), 2.75 (d, J=7 Hz, 6H), 3.0-4.25 (m, 16H), 5.97 (s, 2H), 6.83 (d, J=8 Hz, 1H), 6.93 (dd, J=8 Hz, 1H), 7.02-7.08 (m, 3H), 7.49-7.56 (m, 2H). MS (DCI/NH_3) at m/e 554 $(M+H)^+$. Anal calc'd for $C_{31}H_{43}N_3O_6$• 2.1 TFA: C, 53.31; H, 5.73; N, 5.30. Found: C, 53.50; H, 5.38; N, 5.34.

Example 531

trans, trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(3-pyridyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid

Example 531A

N-butyl-N-(3-pyridyl)-amine

To a solution of 941 mg (10 mmol) of 3-aminopyridine and 0.9 mL of butyraldehyde in 30 mL of CH_3OH was added 10 mL of glacial acetic acid. The mixture was stirred at room temperature for 1 hour, then the reaction was cooled with an ice bath, and 650 mg (10.3 mmol) of sodium cyanoborohydride was added. The ice bath was removed, and the reaction was stirred for 4.5 hours at room temperature. The mixture was poured into 300 mL of 0.67M NaOH(*aq.*), and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were back

extracted with brine (1 x 50 mL), dried over MgSO4, filtered, and concentrated to an oil. The product was isolated via silica gel chromatography, eluting with 3:1 ethyl acetate: hexanes to give 1.18g (79%) of a colorless solid.

Example 531B

trans, trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(3-pyridyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid

The compound of Example 531A was reacted according to the procedures of Example 523, to give the title compound. ^{1}H NMR (D_6-DMSO, 300 MHz) δ 0.80 (t, J=6.4 Hz, 3H), 1.15-1.99 (m, 4H), 2.59 (m, 1H), 3.05 (m, 2H), 3.26 (m, 2H), 3.49 (m, 2H), 3.56 (t, J=7.1 Hz, 2H), 3.73 (s, 3H), 6.00 (s, 2H), 6.80 (m, 3H), 6.85 (d, J=8.1 Hz, 1H), 6.98 (m, 2H), 7.04 (m, 1H), 7.41 (dd, J=1, 4.7 Hz, 8.1H), 7.58 (m, 1H), 8.36 (bs, 1H), 8.54 (bs, 1H), 12.24 (bs, 1H). MS (DCI/NH_3) at m/e 532 $(M+H)^+$. Anal calcd for $C_{30}H_{33}N_3O_6 \cdot 0.1\ H_3PO_4$: C, 66.55. H, 6.20. N, 7.76. Found: C, 66.59; H, 6.06; N, 7.60.

Example 532

trans, trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(3-aminomethylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid

Example 532A

N-butyl-N-(3-hydroxymethylphenyl)-amine

To a solution of 3.69 g (30 mmol) of 3-amino benzyl alcohol in 20 ml DMSO was added 3.78 g (45 mmol) solid $NaHCO_3$ and 2.91 ml (27 mmol) 1-bromobutane. The reaction was allowed to stir at 50 C for 18 hours (overnight). Reaction was worked up by adding 250 ml water and product was extracted in ethyl acetate. Water was added, and the resultant mixture was extracted with EtOAc. The organic layer was washed with water and brine.

Example 532B

N-butyl-N-(3-hydroxymethylphenyl)-bromoacetamide

To a solution of 3.42 g (19.2 mmol) of the compound of Example 532A in 20 ml toluene, was added 2.42 ml (30 mmol) pyridine. The mixture was cooled to 0 C;

4.025 gm (20.0 mmol) of bromoacetyl bromide (diluted with 5 ml toluene) was added in a dropwise fashion.

The reaction mixture was allowed to stir for 5 hours at 0 C and then was allowed to warm to room temperature. Saturated potassium carbonate solution was added, and the mixture was stirred vigorously for 2 hours. The mixture was extracted with EtOAc; the organic layer was washed with 1N H_3PO_4, water, and brine.

Example 532C

Ethyl *trans, trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(3-chloromethylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylate

According to the procedure of Example 523C, N-butyl-N-(3-hydroxymethylphenyl)-bromoacetamide was coupled with ethyl 2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate. The crude product (129 mg) was dissolved in 0.5 ml of DMF and cooled to 0°C; 19 mg of LiCl was added, followed by 85 µl of thionyl chloride. The mixture was allowed to stir for 30 min; water was added, and the mixture was extracted with EtOAc. The organic extracts were washed with water and brine, and dried over Na_2SO_4.

Example 532D

trans, trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(3-aminomethylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid

The compound of Example 532C (182 mg) was dissolved in 1 mL of DMF. Two drops of water were added, followed by 126 mg (2.0 mmol, 6.5 eq) of sodium azide. The resultant solution was heated at 115 °C for 3 hours. Water was added, and the mixture was extracted with EtOAc. The organic extracts were washed with water and brine, and dried over Na_2SO_4.

Example 532E

trans, trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(3-aminomethylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid

In a 50 ml round bottom flask 0.090 gm Tin (II) chloride was suspended in 1 ml acetonitrile. Triethylamine (0.2 mL) was added, followed by 0.19 ml of thiophenol ; the reaction mixture turned yellow. Reaction flask was cooled to 0 C in ice bath; a

solution of 0.185 gm of the compound of Example 532D in 2 ml acetonitrile was added. The mixture was allowed to stir for 30 min. Ether (10 ml) was added, followed by addition of 10 ml 2N HCl . The aqueous extract was basified with 4N NaOH and extracted with dichloromethane. The organic layer was washed with water and brine. The crude product was dissolved in a solution of ethanol and aqueous 2.5 N sodium hydroxide and stirred for 8 hours at room temperature. The solution was concentrated *in vacuo* and water added. The mixture was extracted with ether; the aqueous layer was acidified to pH 4 with 1N H_3PO_4, and the product was purified by preparative HPLC. ^1H NMR (CD_3OD, 300 MHz) δ 0.88 (t, J=7 Hz, 3H), 1.15-1.45 (m, 4H), 3.40-4.20 (m, 14H), 5.97 (s, 2H), 6.82 (d, J=8 Hz, 1H), 6.88 (dd, J=8 Hz, 1H), 6.97-7.20 (m, 5H), 7.40 (d, J=9 Hz, 2H), 7.56 (d, J=5 Hz, 2H). MS (DCI/NH_3) at m/e 560 $(M+H)^+$. Anal calcd for $C_{32}H_{37}N_3O_6 \cdot 4.2$ TFA: C, 46.72; H, 4.00; N, 4.05. Found: C, 46.66; H, 4.06; N, 4.00.

Example 533

trans, trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(3-trimethylammoniomethylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid

To a stirred solution of 0.128 gm of the compound of Example 532C in 0.5 ml methanol, 0.25 ml of an aqueous solution of trimethylamine was added. The mixture was allowed to stir at room temperature under nitrogen atmosphere for 4 hours. 1N HCl was added; the aqueous was washed with ether to extract organic impurities. The aqueous layer was dried azeotropically with toluene, and the residue was dried under high vacuum. Yield 0.115 gm. ^1H NMR (300 MHz, D6-DMSO) δ 0.83 (t, J=7 Hz, 3H), 1.15-1.40 (m, 4H), 2.62 (s, 2H), 3.35 (s, 9H), 3.40-3.80 (m, 10H), 4.47 (s, 2H), 6.00 (s, J=3 Hz, 2H), 6.75-6.90 (m, 3H), 7.25-7.37 (m, 2H), 7.45-7.60 (m, 3H). MS (DCI/NH_3) at m/e 602 $(M+H)^+$.

Example 534

(2R,3R,4S)-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)1-(2-(N-propyl-N-pentanesulfonylamino)ethyl)-pyrrolidine-3-carboxylic acid

Example 534A

Ethyl (3-fluoro-4-methoxy)benzoylacetate

Sodium hydride (17g of a 60% suspension in mineral oil) is washed three times with toluene. The powder is suspended in 138 mL of toluene, and 35 mL of diethyl carbonate is added. The mixture is heated to 90 °C, and a solution of 25 g of 3-fluoro-4-methoxyacetophenone and 50 ml of diethyl carbonate in 50 ml of toluene was added portionwise. Heating is continued for 30 min, then the reaction is cooled to room temperature. A solution of 50 ml of concentrated HCl in 75 ml of ice water is added slowly, and the mixture is stirred. The mixture is extracted with toluene; the combined organic extracts are washed with brine and bicarbonate solutions. The product is dried over Na_2SO_4 and decolorized with charcoal to give 34.5 g (97%) of the title compound.

Example 534B

Ethyl 2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate

The compound of Example 534A (12.5 g) and 5-(nitrovinyl)-1,3-benzodioxole (13.1 g, 20% excess) were suspended in a mixture of 75 ml of THF and 13 ml of iPrOH. DBU (0.25 g) was added, and the mixture was stirred at room temperature for 30 min. An additional 0.1 g of DBU was added, and the solution was stirred for 1 hour. The solvents were removed in vacuo; toluene was added, along with brine containing 3 ml of concentrated HCl. The mixture was extracted twice with toluene; the organics were dried over $MgSO_4$. The residue was flashed on silica, using CH_2Cl_2 to elute. Yield 75%. This material (17.4 g) is combined with 35 g of Raney Nickel (washed) in 250 mL of EtOAc. The mixture is shaken under 4 atm of hydrogen for 18 hours. The solution is concentrated in vacuo; the residue is chromatographed on silica, eluting with 4% EtOAc in CH_2Cl_2. Yield 10.13 g = 66%. The product is combined with 26 ml of THF and 50 ml of EtOH; 2.18 g of $NaBH_3CN$ are added, along with a trace of bromcresol green as indicator. A solution of 1:2 concentrated HCl/EtOH is added dropwise to maintain pH at green-yellow; after color persists, the reaction mixture is stirred for an additional 20 min. The solvents are removed in vacuo; the residue is stirred with mixture of toluene and $KHCO_3$ solution. The organic phase is washed with water and brine, and dried over $MgSO_4$. The crude product is purified by flash chromatography on silica, eluting with 2:1 EtOAc/hexanes. Yield 5.92 g (58%) of a 2:1 mixture of trans-trans and cis-trans isomers.

Example 534C

Ethyl (*2R,3R,4S*)-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate

To the racemic amino ester above (15.0 g, 38.8 mmol), dissolved in 75 ml methylene chloride and cooled in an ice bath, was added Boc anhydride (9.30 g, 42.7 mmol). After stirring 2 hours at room temperature, the solution was concentrated *in vacuo* ; the residue was dissolved in 50 ml ethanol and treated with a solution of 3.75 g sodium hyroxide in 19 ml water. The solution was warmed until all was soluble. After stirring for 2 hours at room temperature, the solution was concentrated and redissolved in 200 ml of water. This was extracted with 75 ml of diethyl ether. The ether layer was extracted with 40 ml of water. The combined aqueous phases were acidified with 7.5 g acetic acid; the mixture was stirred until a solid formed. The solid was filtered, washed with water and dissolved in methylene chloride. After drying with sodium sulfate, the solution was concentrated and the residue crystallized from 1:1 ether:hexane to get 15.99 g of product, m.p. 200-203 (90% yield). The crude acid was suspended in 80 ml ethyl acetate and treated with 4.00 g (33.1 mmol) of (S)-(-)-a-methylbenzylamine. After heating to dissolve the acid, 80 ml of ether was added. Scratching with a glass rod caused the product to crystallize. The solids were filtered and washed with ether-ethyl acetate solution to give 8.22 g (81% yield based on 50% maximum recovery) of salt, m.p. 165-168°C. After one recrystallization, chiral HPLC analysis, using a Regis Whelk-O column, indicated >99.5 % e.e. The salt was dissolved in 500 ml of 36% HCl in ethanol; a white solid forms. The resultant suspension was heated for 16 hours at 52°C. After concentrating *in vacuo*, the residue was combined with toluene and stirred with potassium bicarbonate in water for 30 minutes. The toluene was separated, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel, eluting with 33% hexane-67% ethyl acetate to get 6.9 g (99%) of the resolved amino ester.

Example 534D

Ethyl *(2R,3R,4S)*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)1-(2-(N-propylamino)ethyl)-pyrrolidine-3-carboxylate

The compound of Example 534C was dissolved in 1,2-dibromoethane (10 mL per 1 g of starting material); diisopropylethylamine (1 mL per 1 g of starting

material) and NaI (100 mg per 1 g of starting material) were added, and the mixture was stirred at 100°C for 1 hour. Toluene was added, and the mixture was washed with bicarbonate. The solvents were concentrated, and the resultant black residue was chromatographed on silica gel, eluting with 4:1 hexane-EtOAc to give the N-(2-bromoethyl)pyrrolidine (85-92%). This compound was combined with n-propylamine (3.5 eq.) and NaI (10% by weight of bromide) in ethanol (5 mL per 1 g of bromide), and was heated at 80°C for 2 hours. Toluene was added, and the mixture was washed with bicarbonate, dried (Na_2SO_4), and concentrated. More toluene was added, and removed *in vacuo*, to get rid of the primary amine. The residue was dissolved in heptane and filtered to remove a small amount of insoluble material. Evaporation of the solvent gave the desired product (86-93% yield), which was used for the next step without further purification.

Example 534E
1-Pentanesulfonyl chloride

1-Pentanesulfonic acid, sodium salt (10 g, 57.5 mmol) was charged into a 250 ml round bottom flask (allow headroom). Thionyl chloride (20 mL) is added; gas evolves, and a while solid forms. The mixture is heated at 60 °C for 3 hours. The solvents are removed in vacuo; toluene is added and removed in vacuo to remove residue of $SOCl_2$. The residue is partitioned between CH_2Cl_2 and ice water; the organic layer is dried over Na_2SO_4 . The crude product is purified by distillation (bp 54-56 °C @ 0.5 mm Hg) to give a clear oil, 61% yield.

Example 534F
(2R,3R,4S)-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)1-(2-(N-propyl-N-pentanesulfonylamino)ethyl)-pyrrolidine-3-carboxylic acid

The compound of Example 534D (200 mg, 0.43 mmol) was dissolved in 5 mL of CH_3CN; 110 mg (2 eq) of N,N-diisopropylethylamine and 72.8 mg (1.2 eq) of 1-pentanesulfonyl chloride were added sequentially, the resultant solution was allowed to stir at room temperature for 30 min. The solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1N H_3PO_4, and brine, dried over Na_2SO_4 and evaporated to give a yellowish oil which was purified by flash chromatography on silica gel eluting with 40% EtOAc/hexane to give 220 mg of product (85%). This

ester was dissolved in 5 mL of EtOH, to which was added NaOH (46 mg, 3 eq) solution in 2 mL of H_2O. This mixture was stirred for 3 hours at room temperature. The solution was concentrated in vacuo using low (<40°C) heat. Water (10 mL) and ether (50 mL) were added; the ether layer was extracted with 5 mL of water. The combined aqueous mixture was back-extracted with ether and then neutralized with acetic acid. This solution was extracted twice with ether. The ether was dried (Na_2SO_4) and concentrated in vacuo. EtOAc (1 mL) and ether (1 mL) were added to dissolve the product, and hexane was added dropwise to produce a white solid. The solid was collected and dried in vacuo to give 125 mg of the title compound.

Example 534H

(2R,3R,4S)-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)1-(2-(N-propyl-N-pentanesulfonylamino)ethyl)-pyrrolidine-3-carboxylic acid, hydrochloride salt

The free amine is dissolved in iPrOH; a slight excess of HCl in iPrOH is added, and the solution is concentrated in vacuo. More IPA is added, and the solution is reconcentrated. The resultant sticky material is stirred with ether overnight to give a white powder, which is collected by filtration and dried overnight in vacuo at 60 °C. Yield 95%.

Example 535

The compounds in Table 3C may be prepared using methods presented in the above Examples.

Table 3C.

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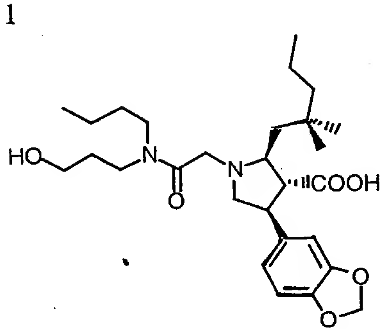

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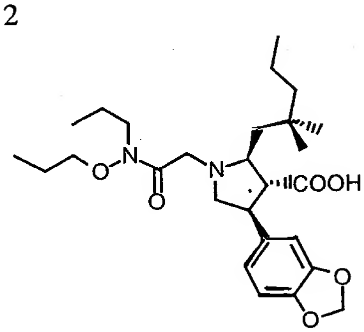

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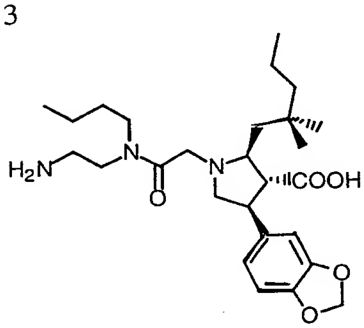

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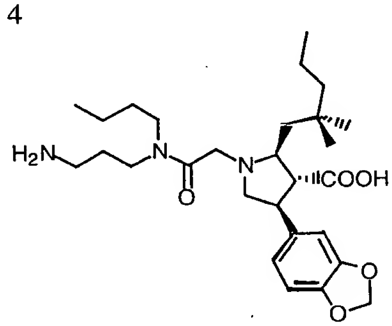

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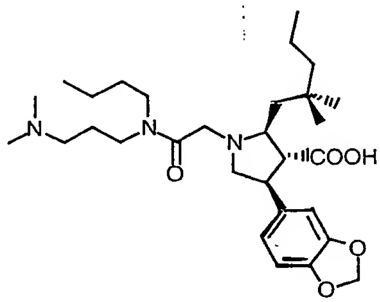

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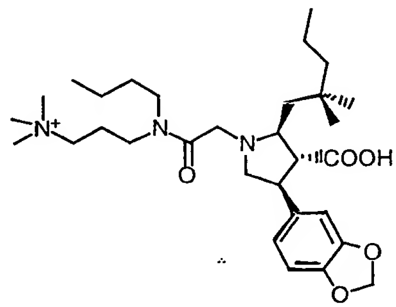

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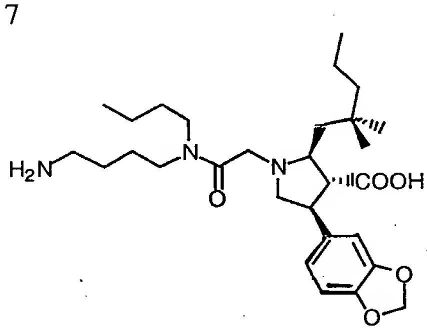

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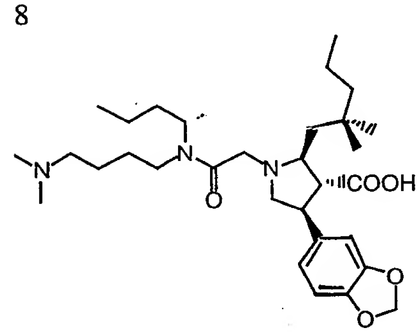

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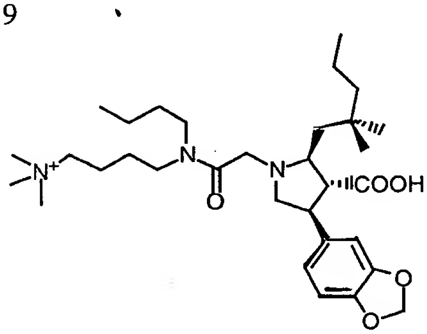

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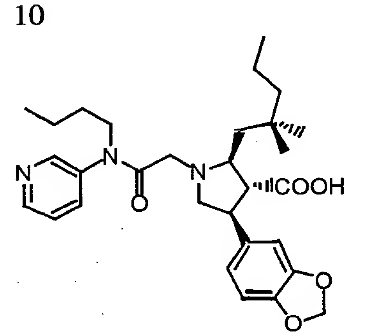

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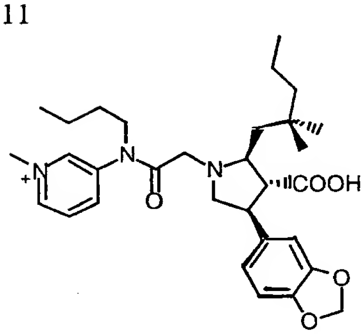

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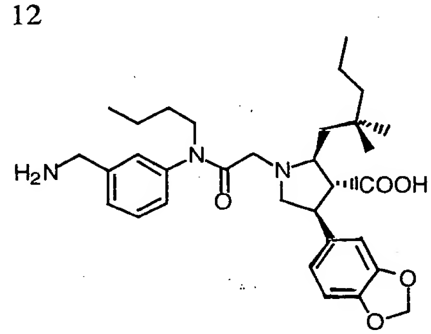

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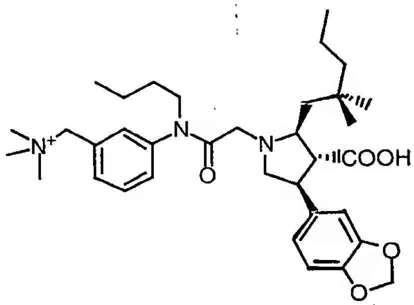

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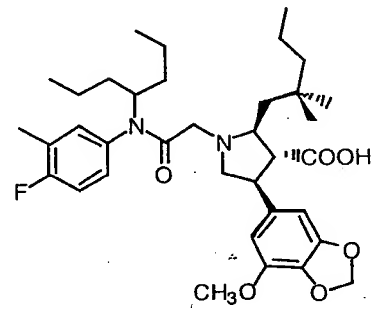

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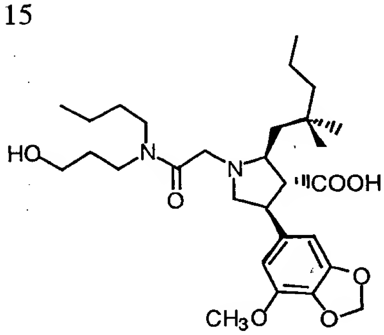

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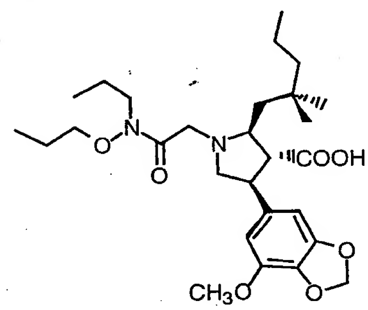

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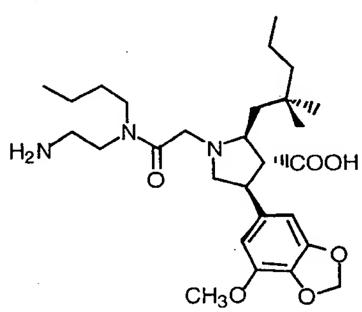

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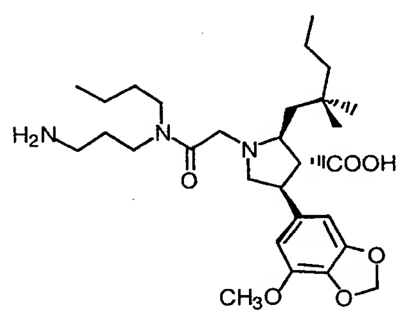

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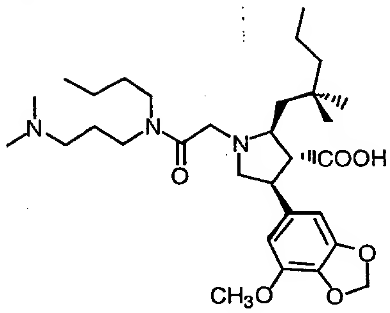

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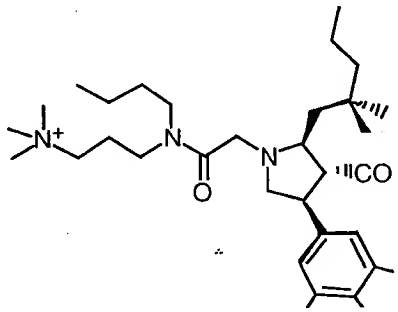

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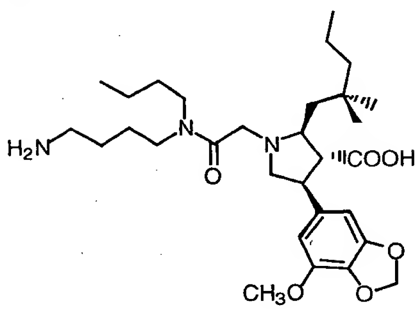

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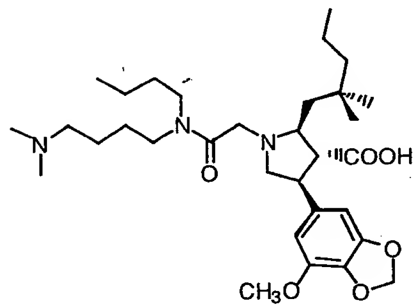

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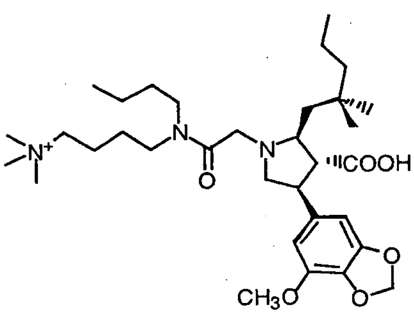

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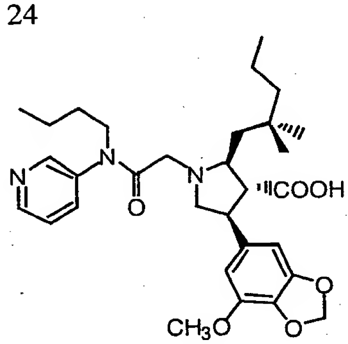

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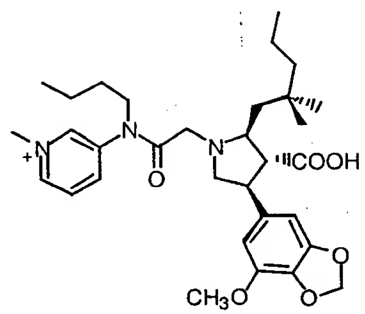

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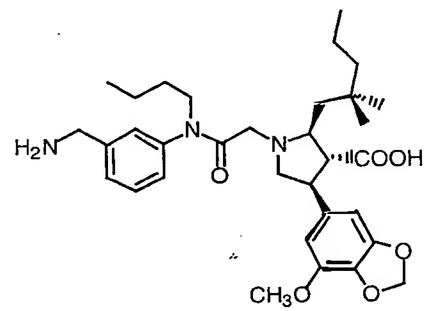

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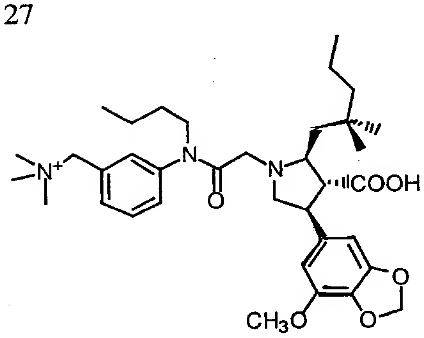

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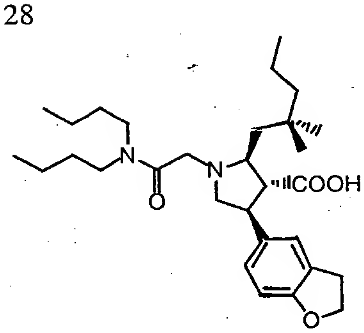

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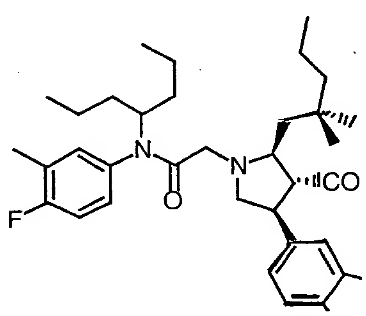

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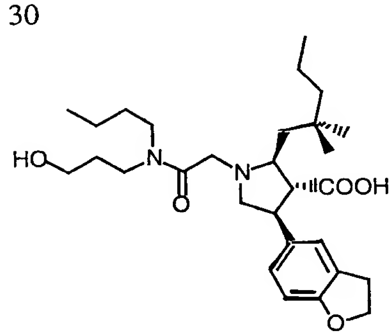

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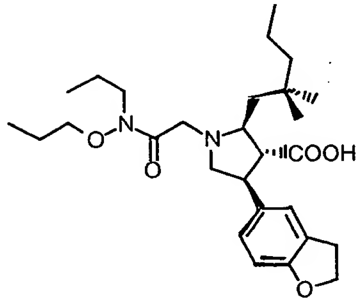

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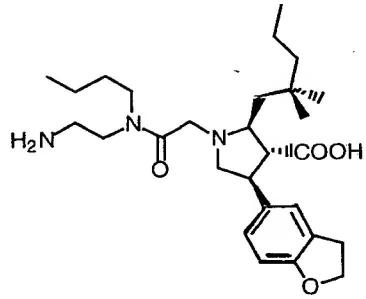

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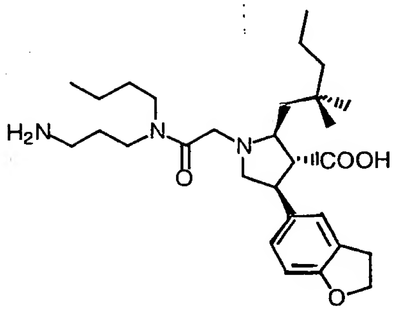

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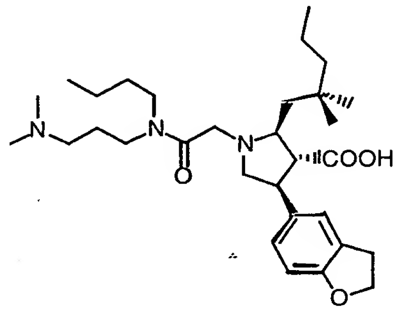

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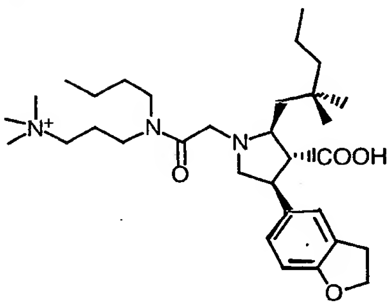

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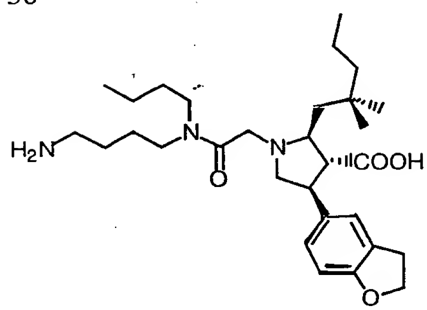

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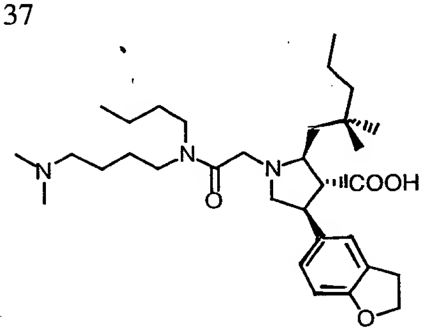

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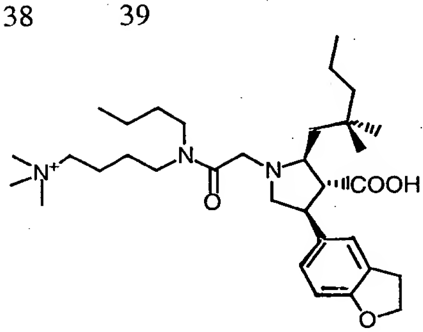

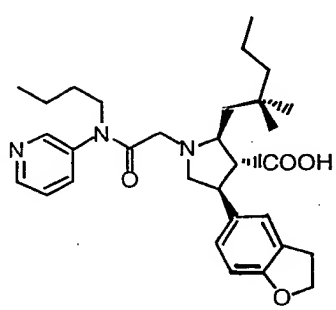

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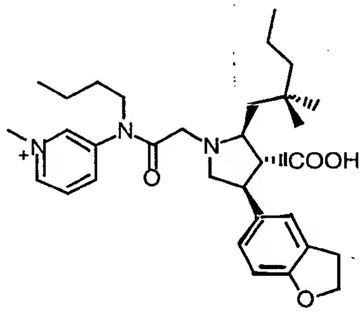

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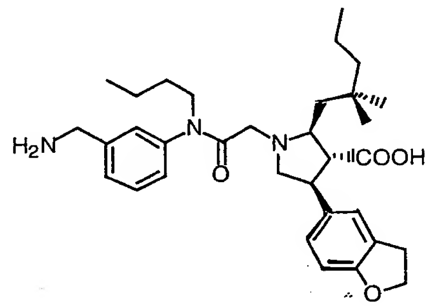

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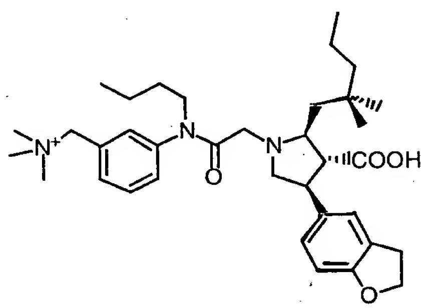

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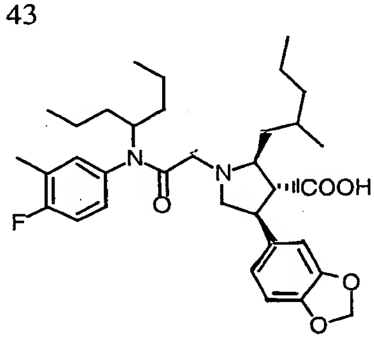

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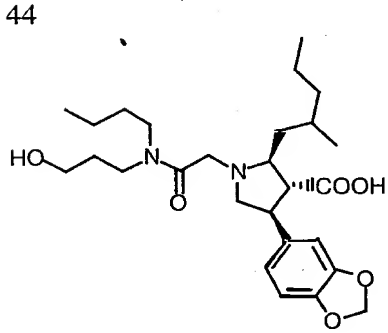

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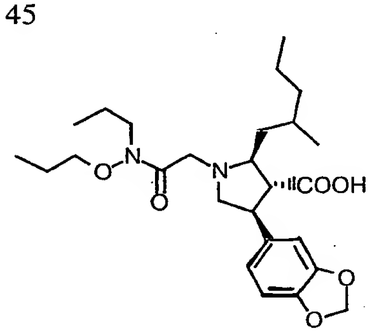

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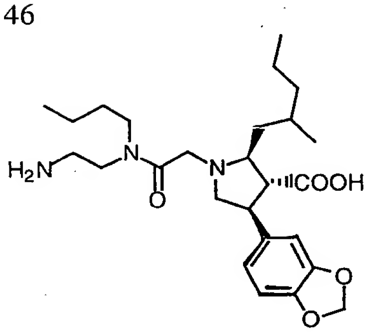

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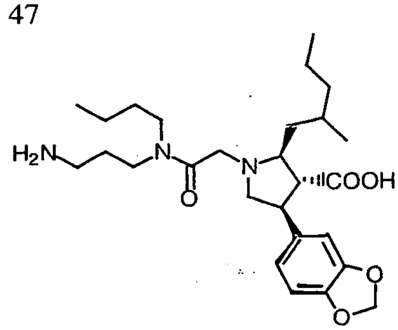

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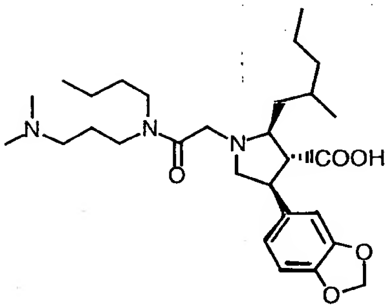

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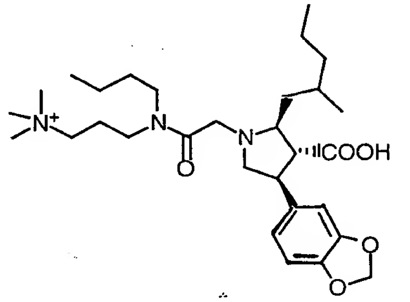

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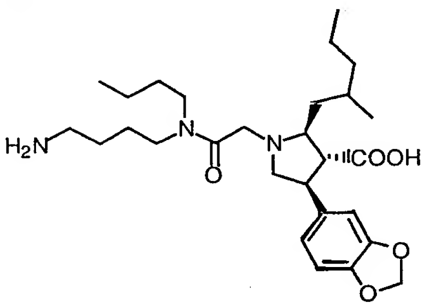

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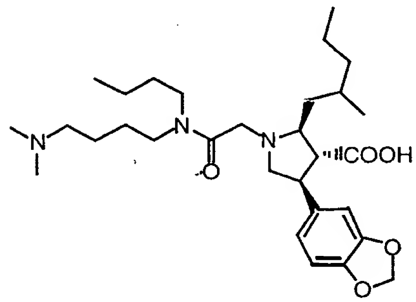

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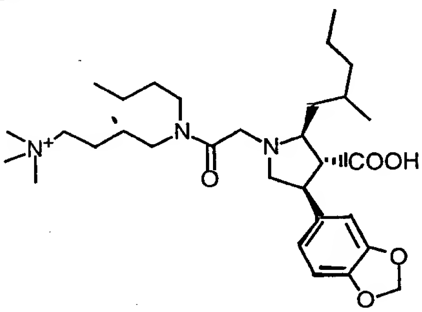

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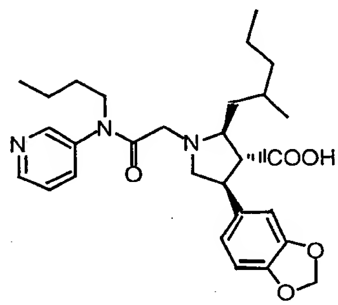

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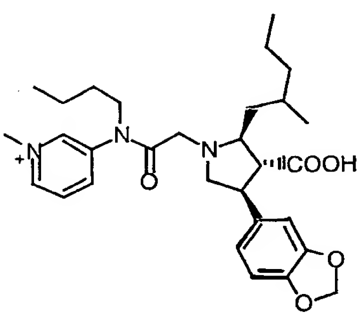

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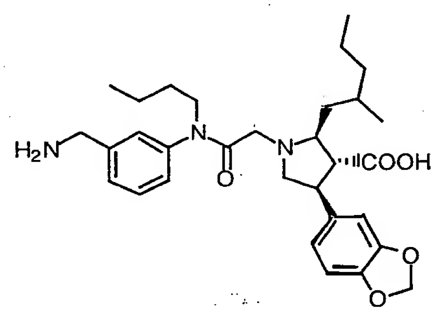

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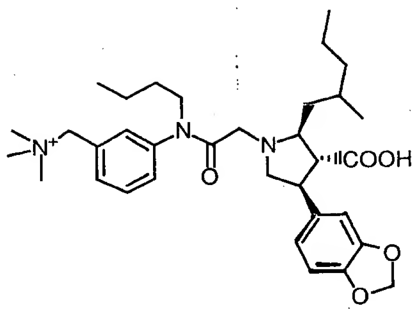

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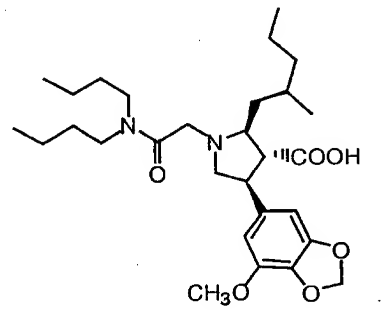

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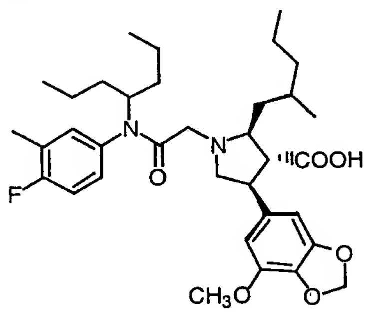

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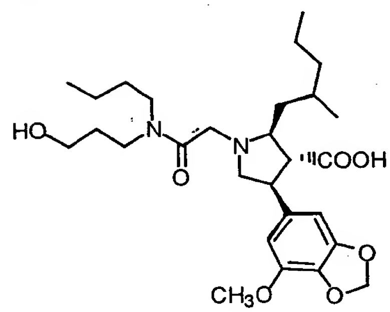

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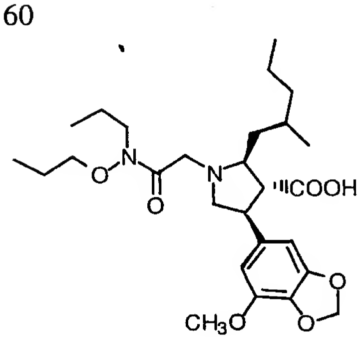

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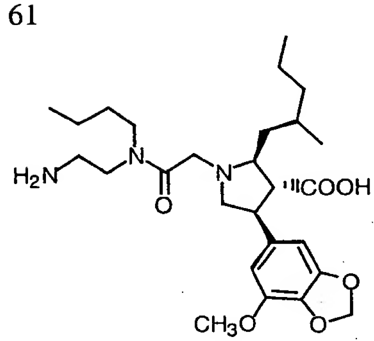

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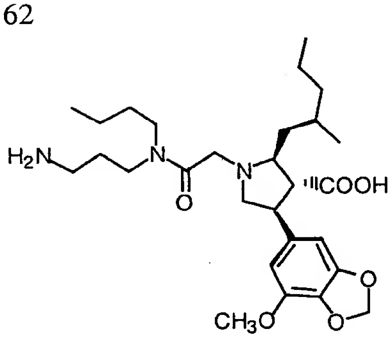

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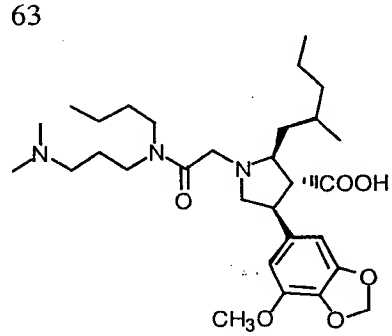

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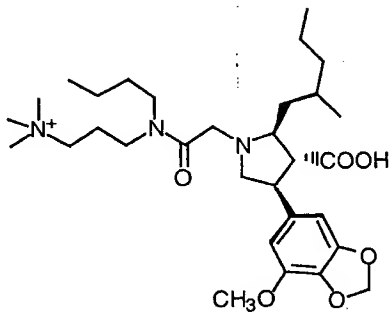

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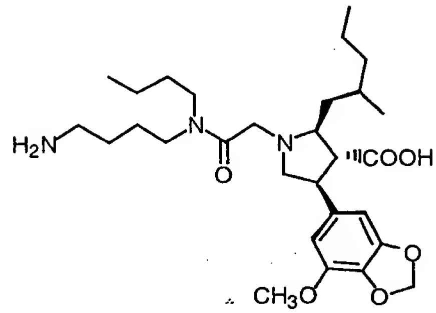

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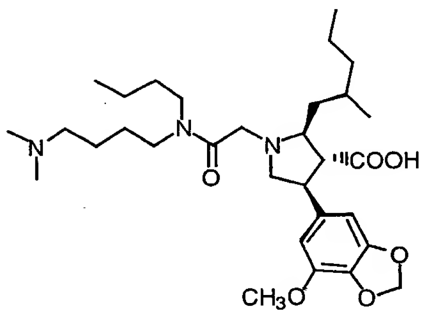

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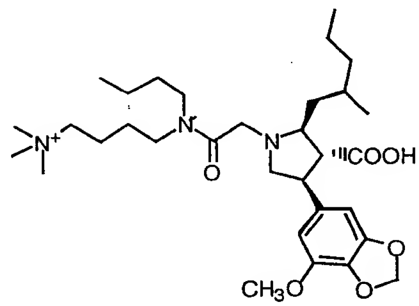

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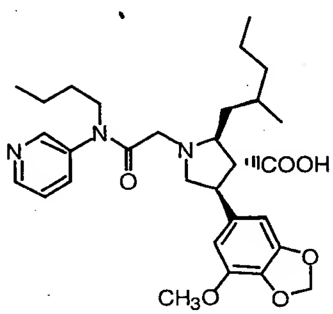

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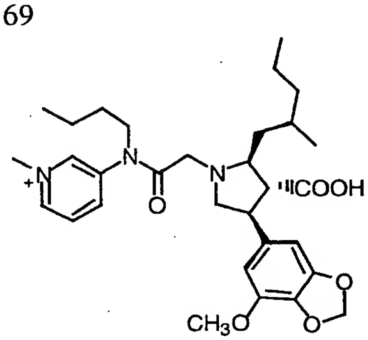

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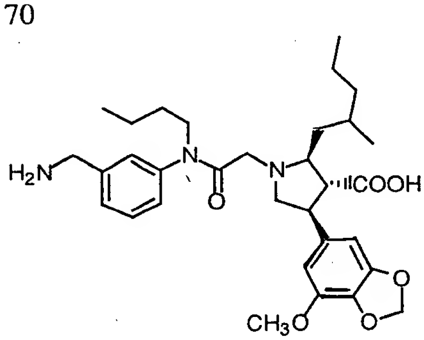

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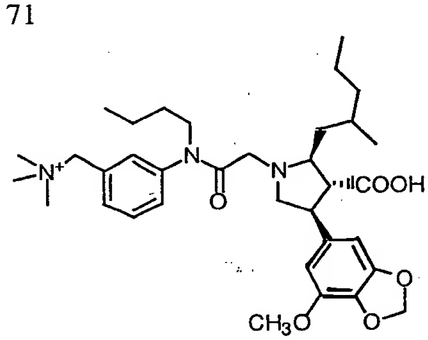

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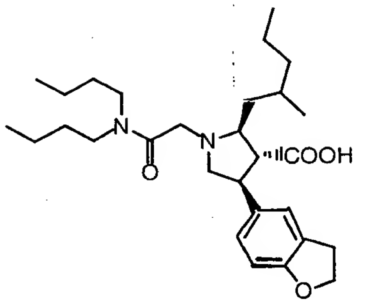

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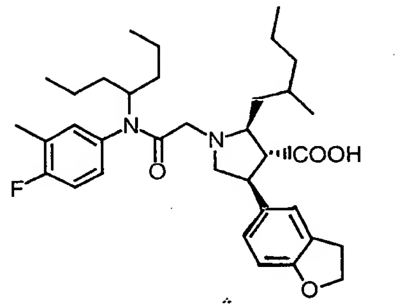

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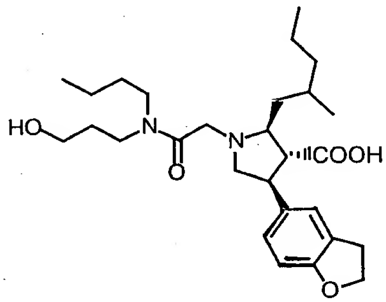

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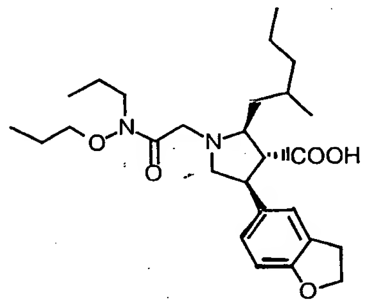

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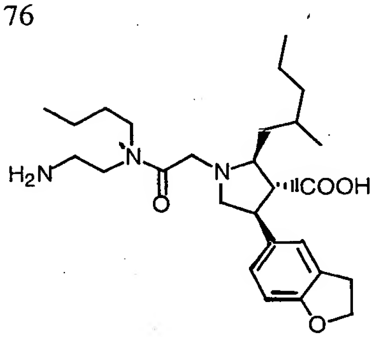

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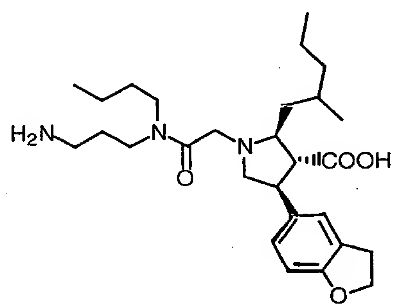

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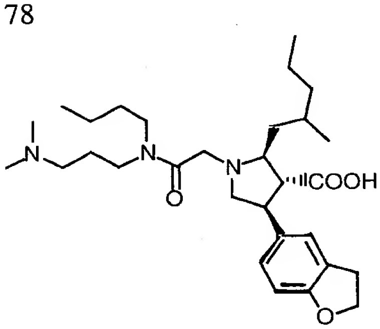

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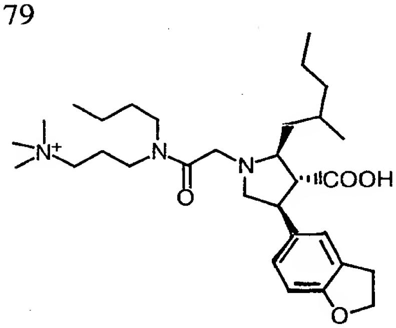

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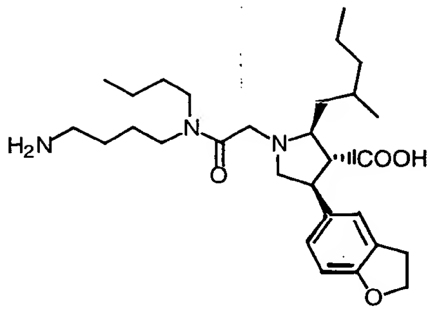

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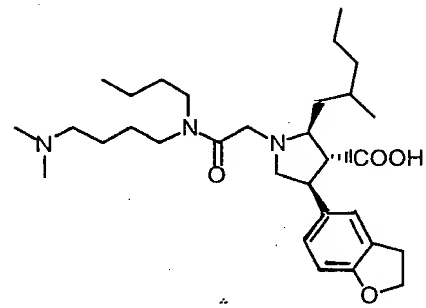

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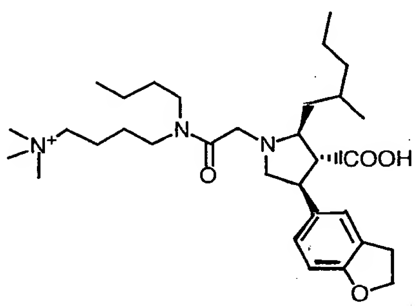

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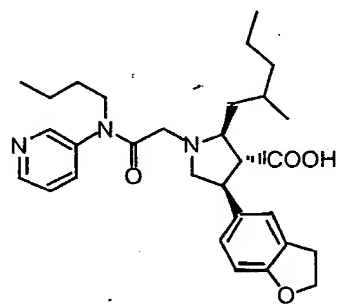

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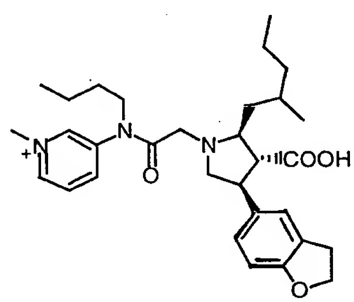

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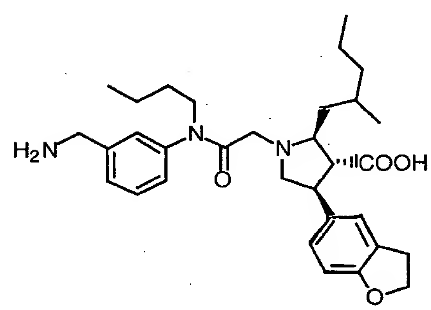

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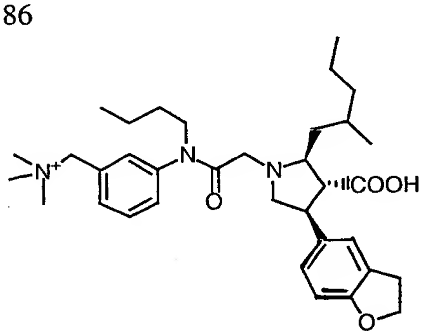

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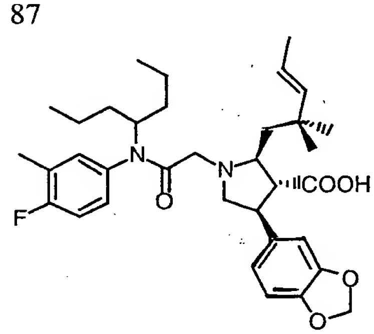

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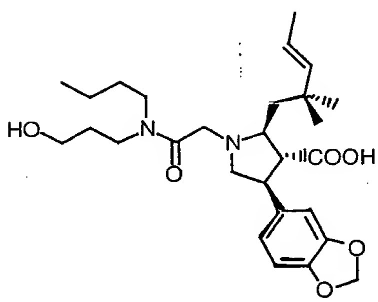

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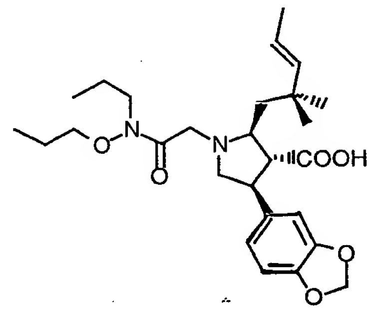

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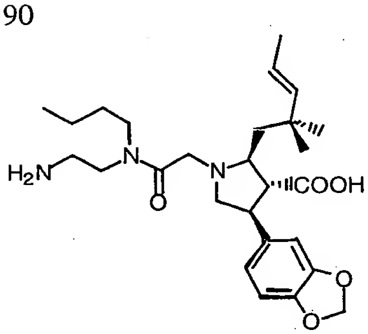

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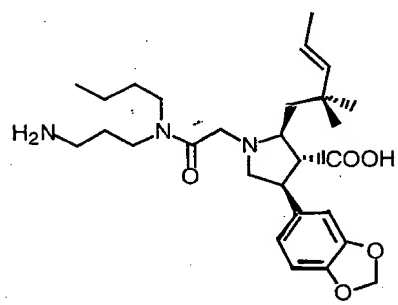

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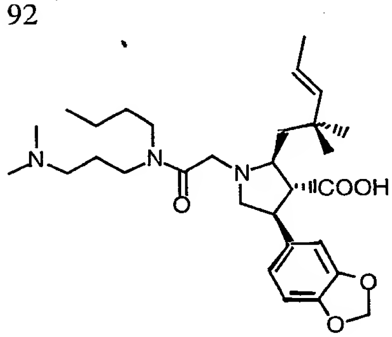

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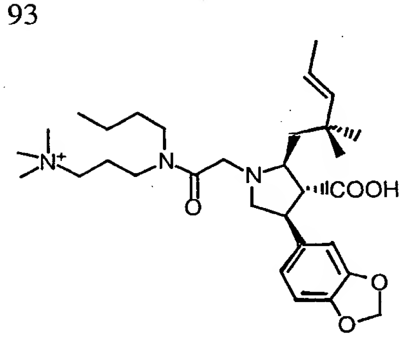

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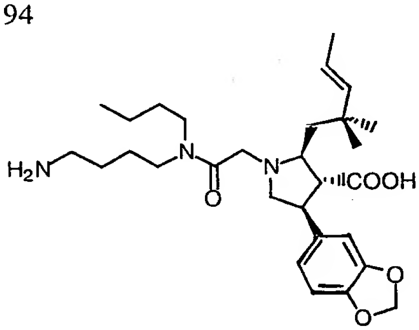

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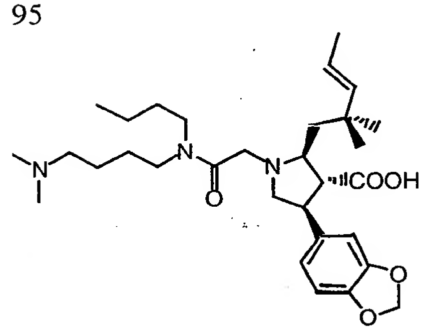

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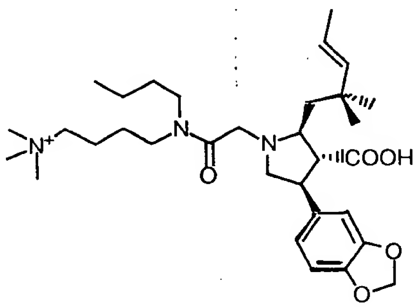

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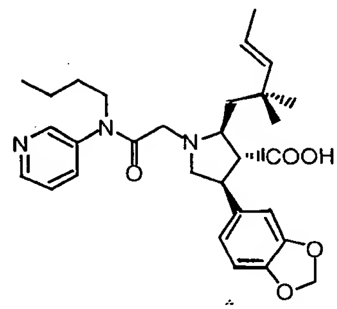

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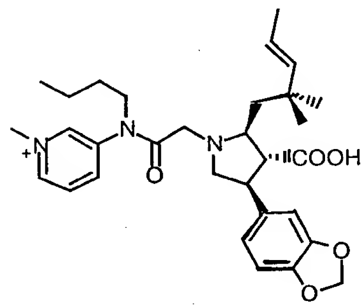

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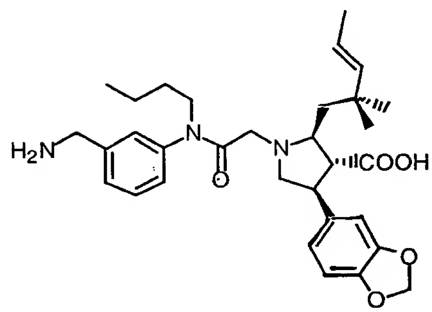

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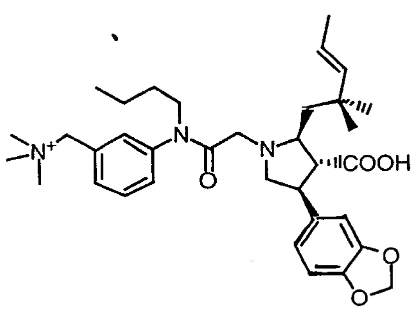

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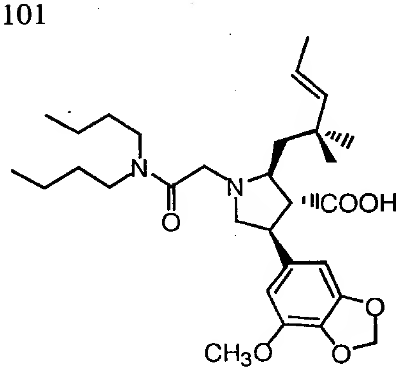

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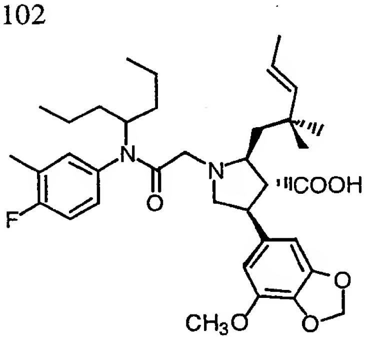

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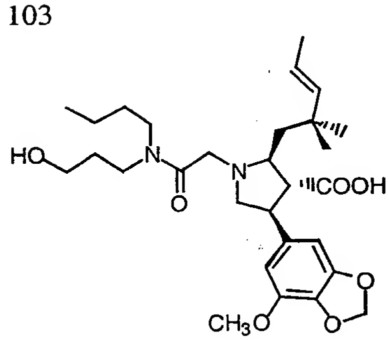

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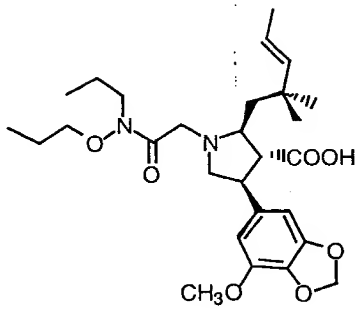

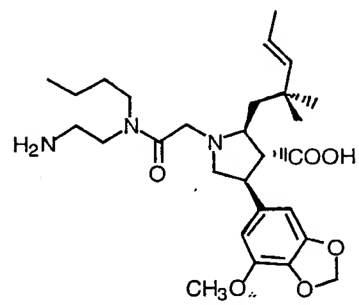

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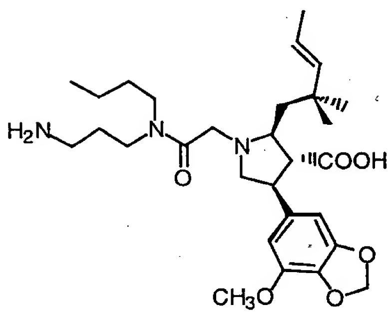

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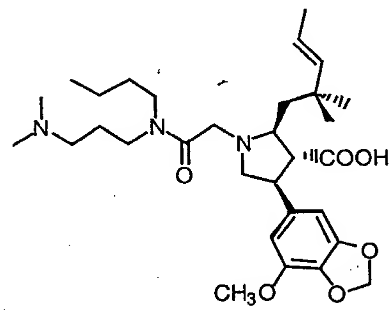

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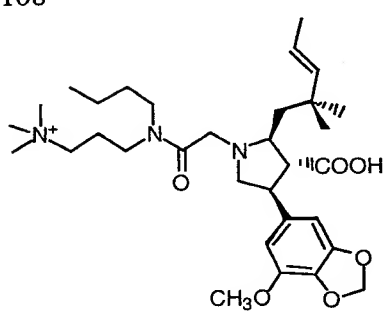

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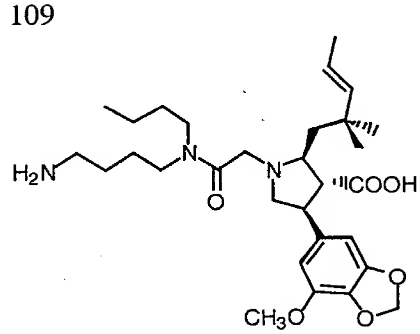

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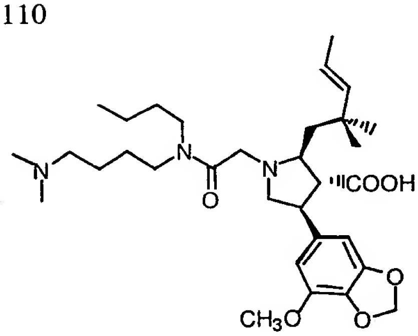

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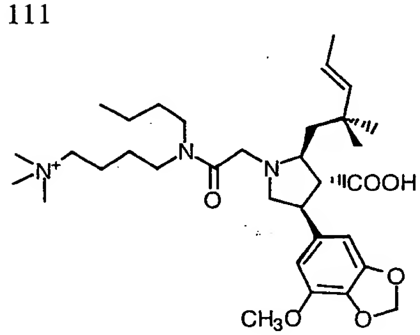

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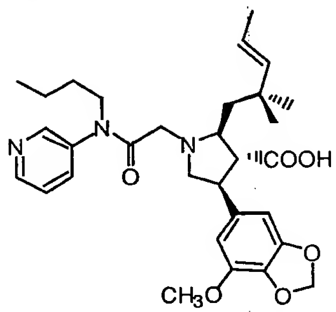

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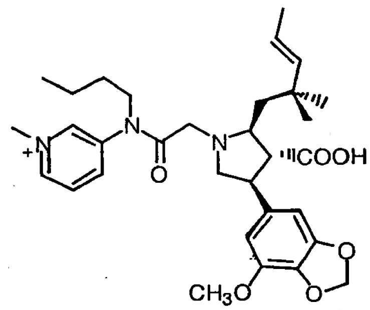

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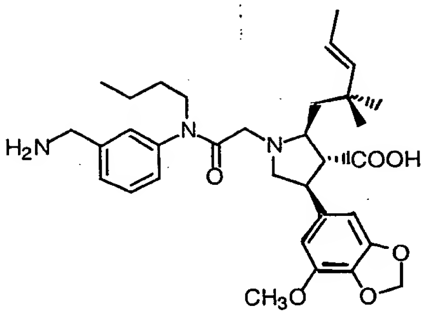

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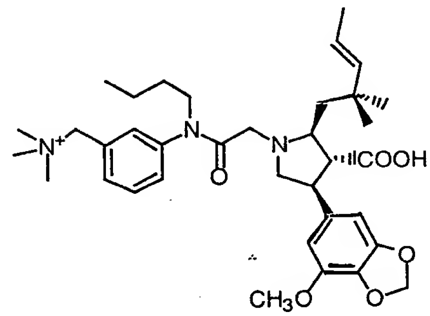

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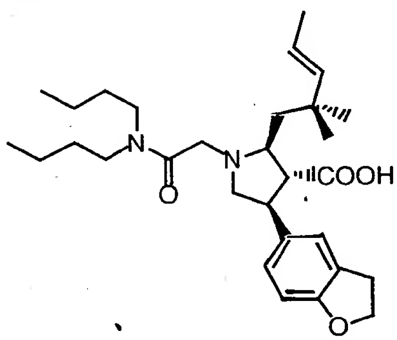

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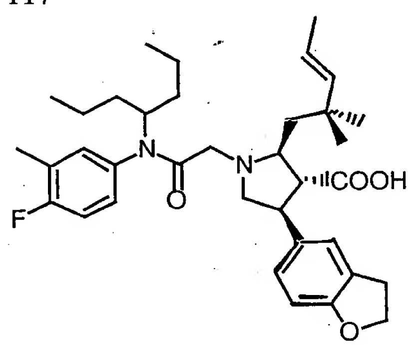

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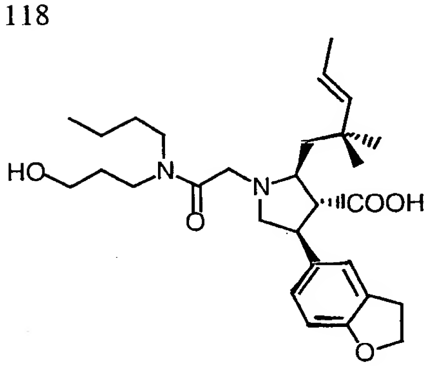

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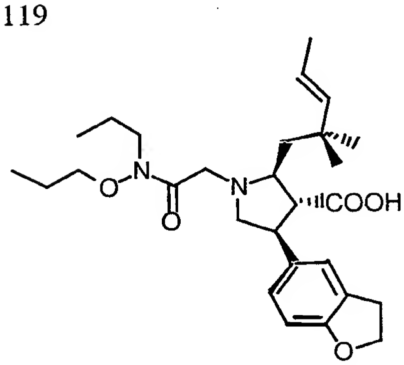

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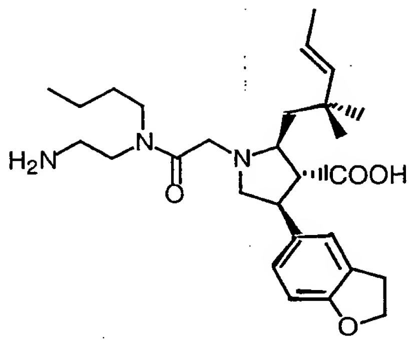

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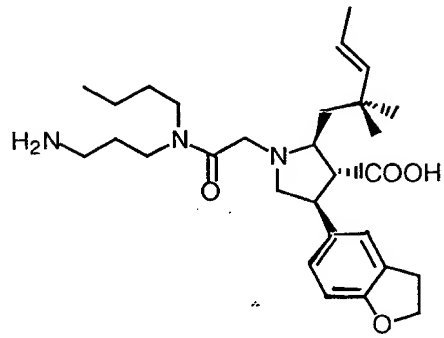

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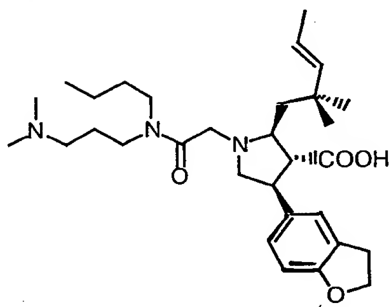

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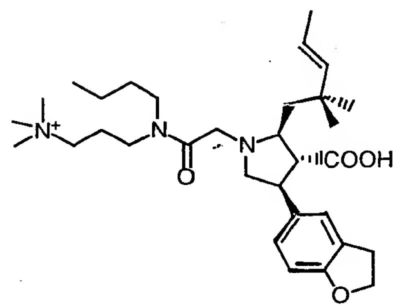

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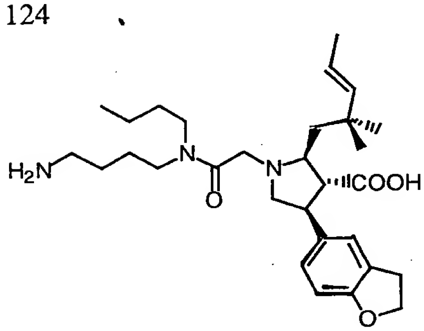

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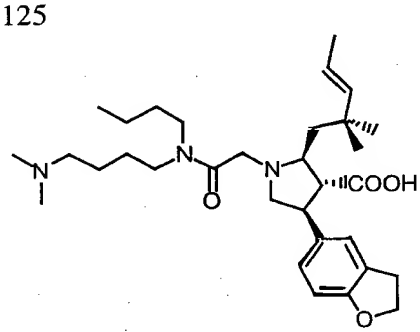

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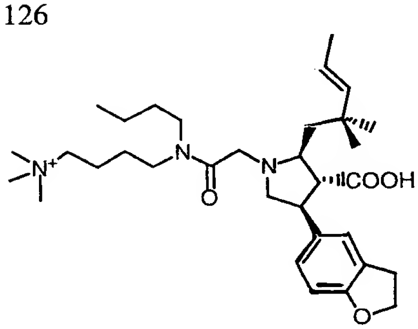

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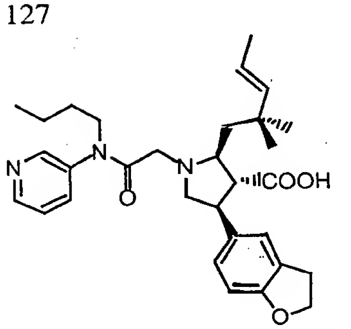

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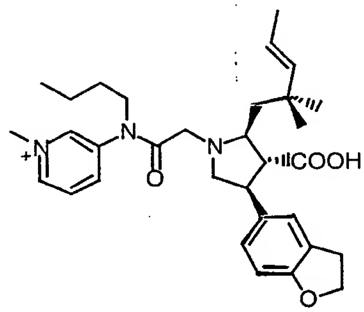

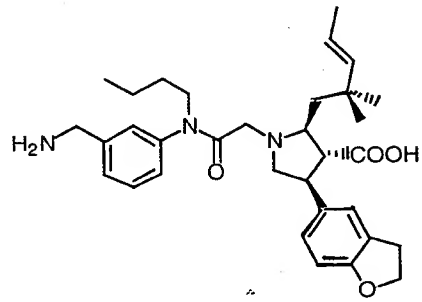

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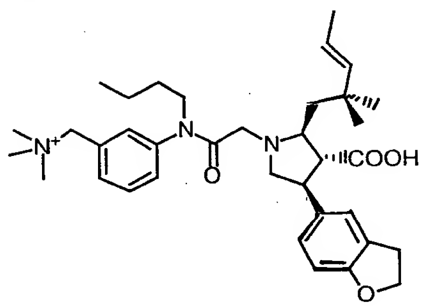

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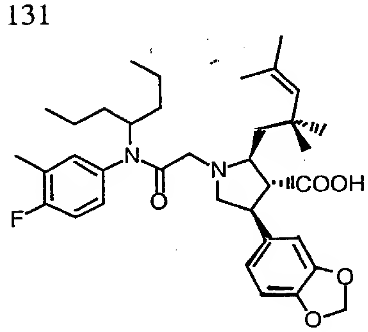

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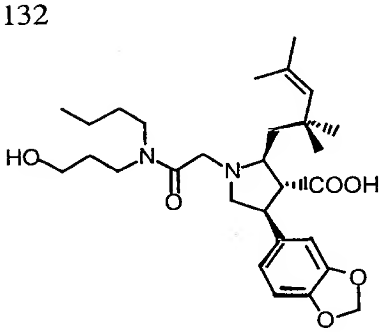

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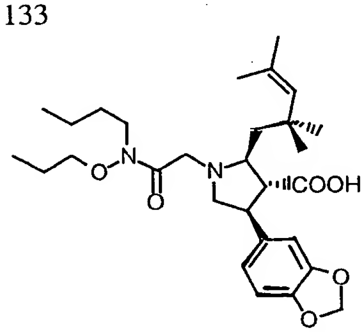

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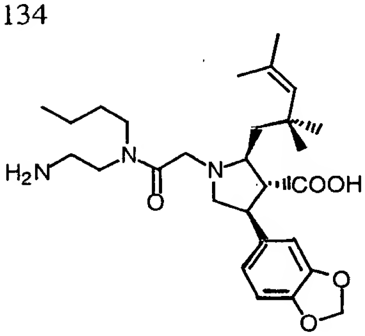

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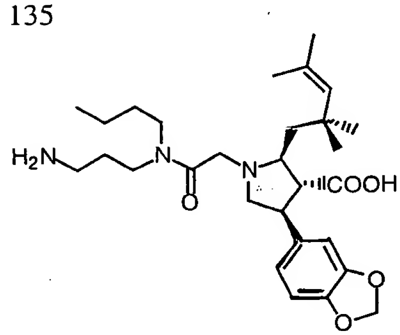

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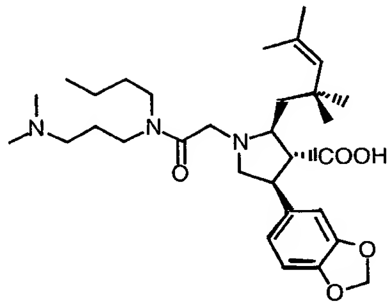

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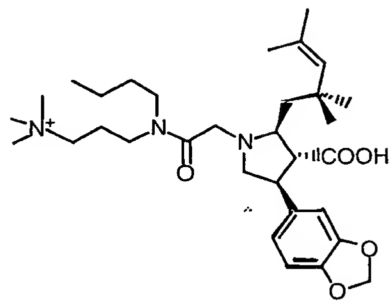

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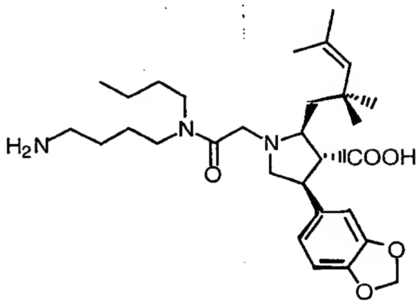

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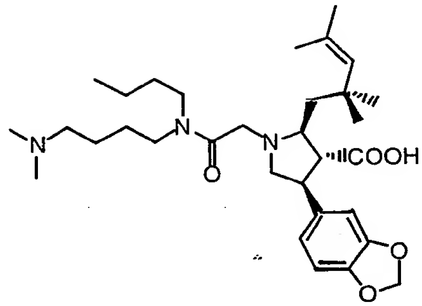

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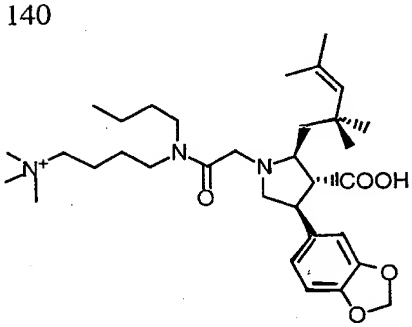

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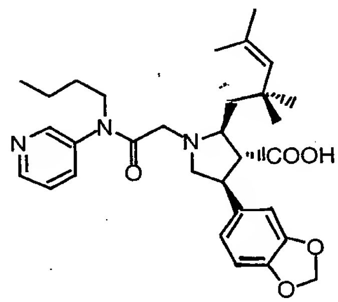

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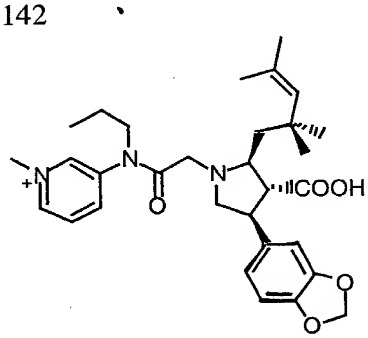

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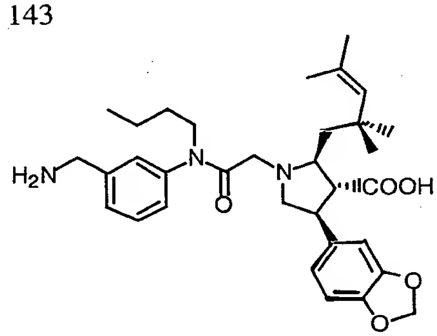

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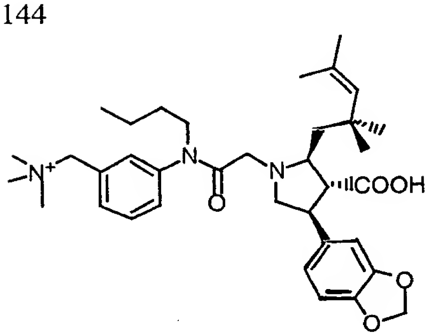

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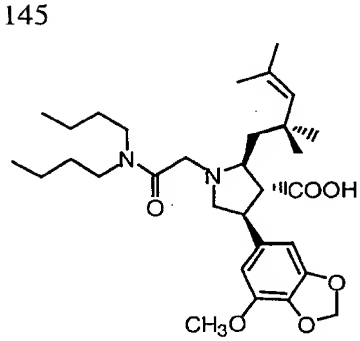

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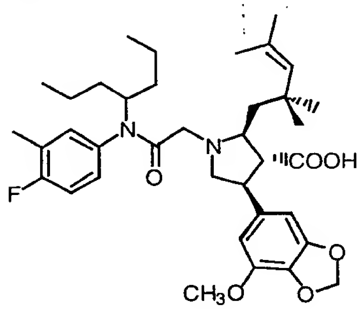

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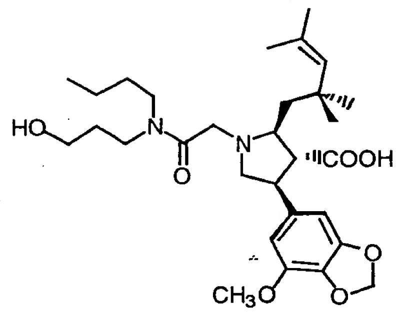

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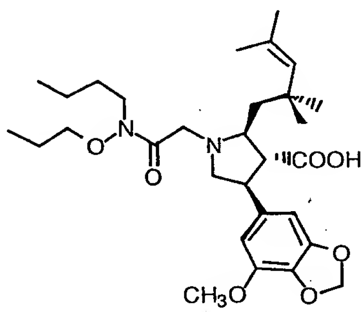

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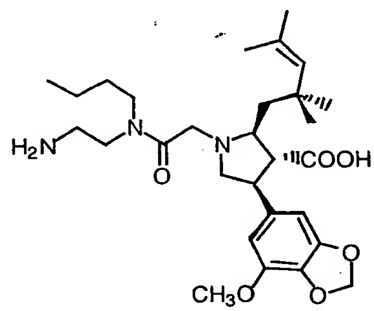

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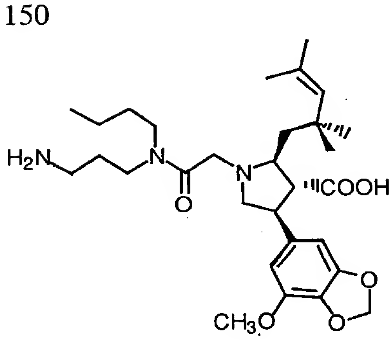

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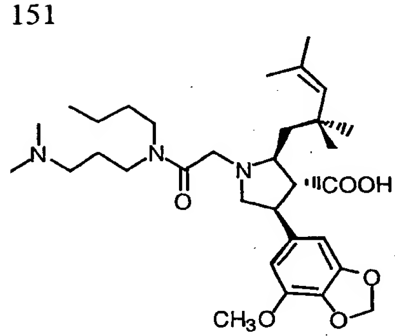

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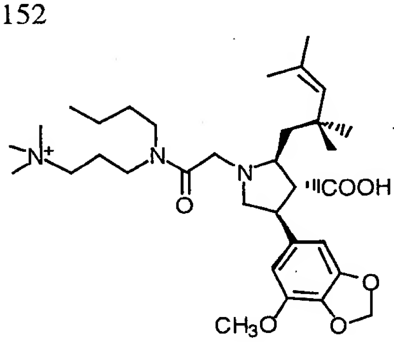

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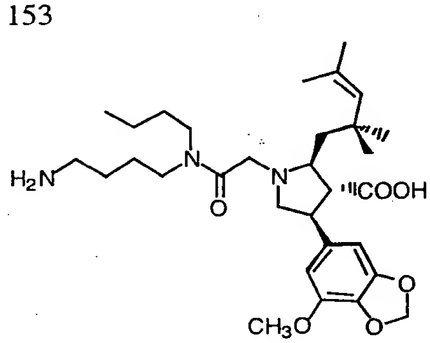

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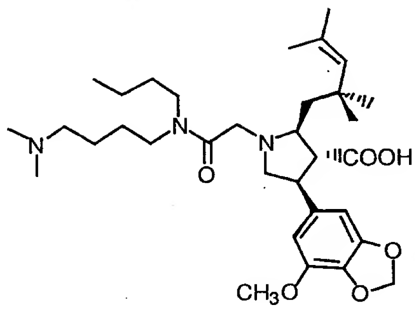

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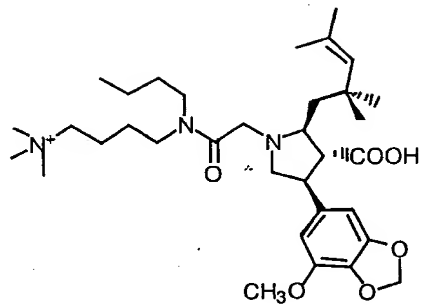

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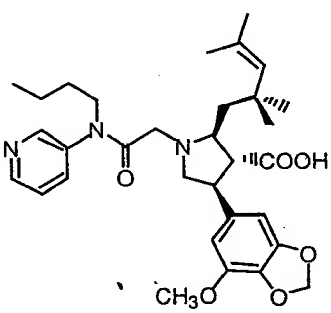

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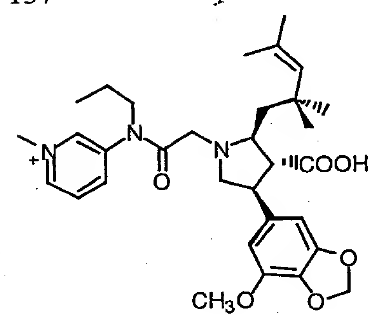

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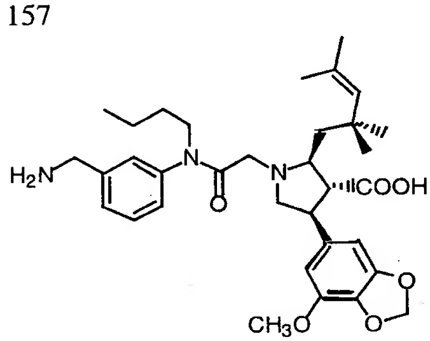

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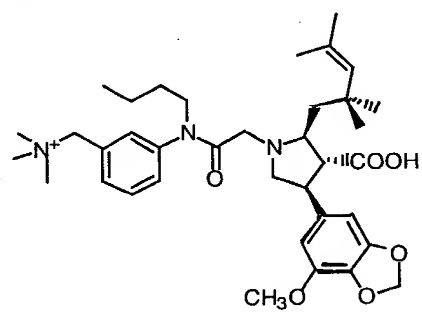

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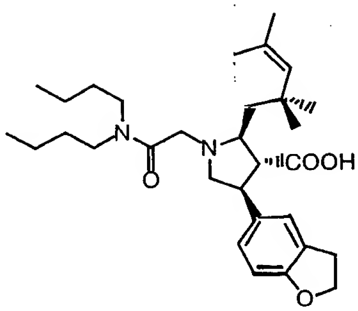

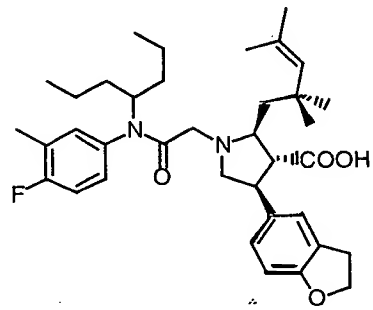

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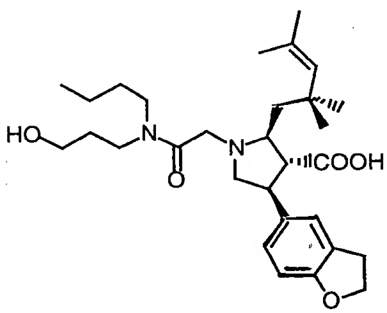

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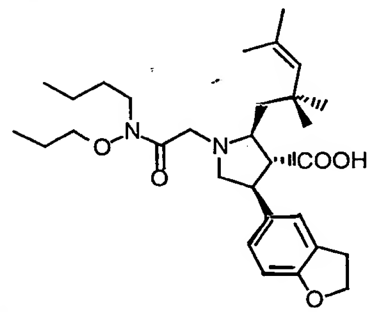

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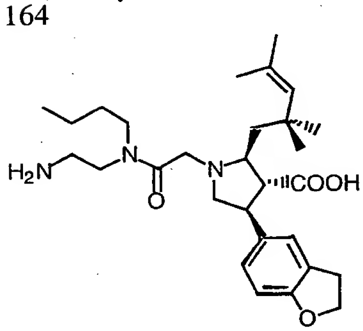

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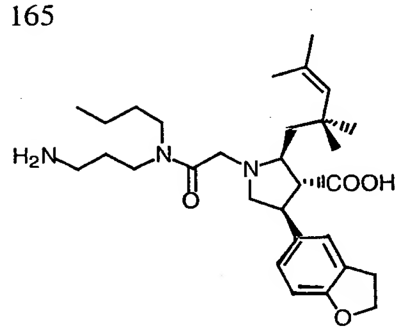

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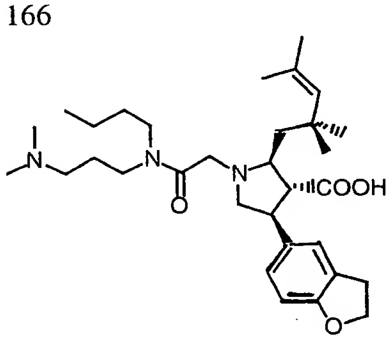

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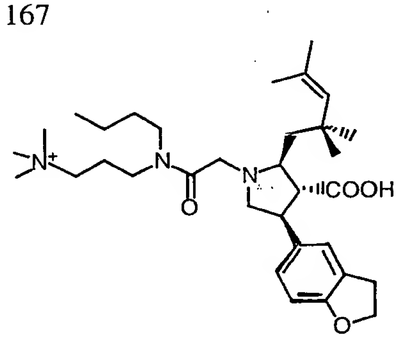

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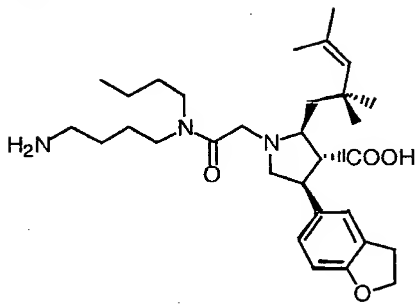

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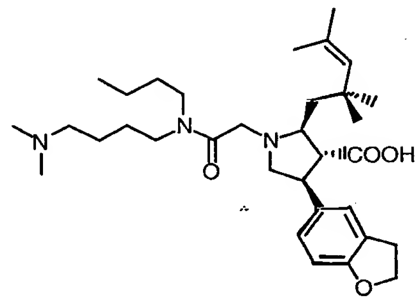

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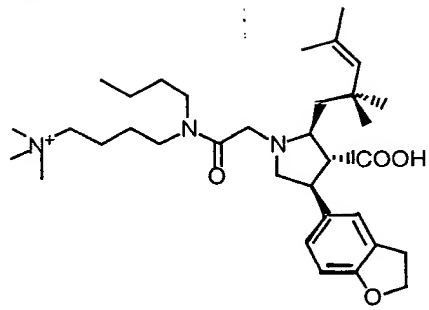

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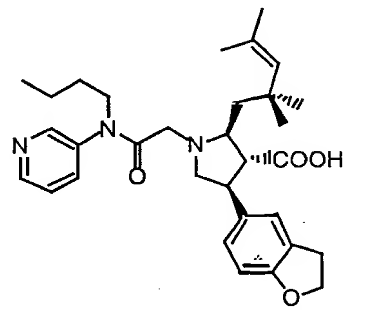

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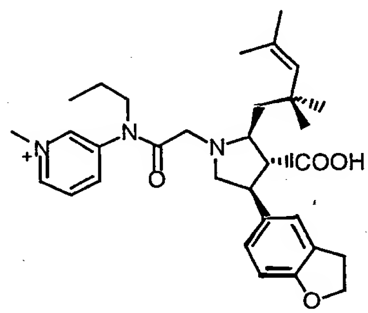

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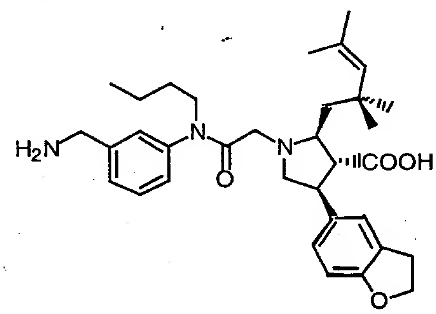

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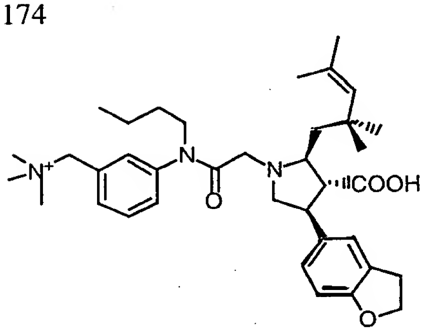

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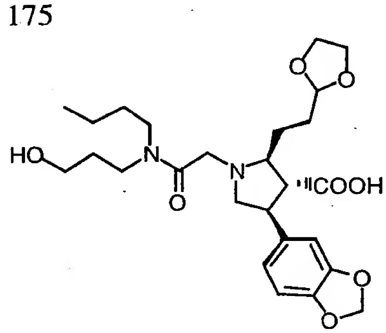

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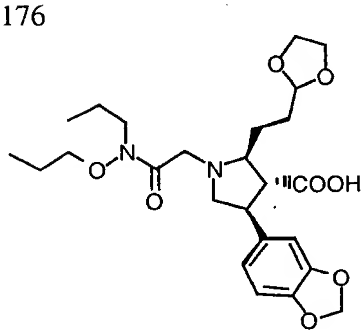

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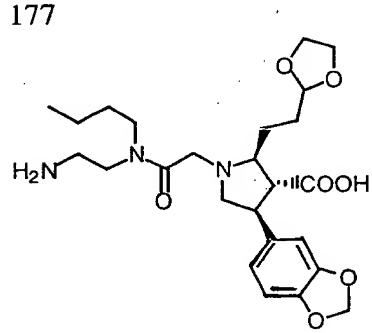

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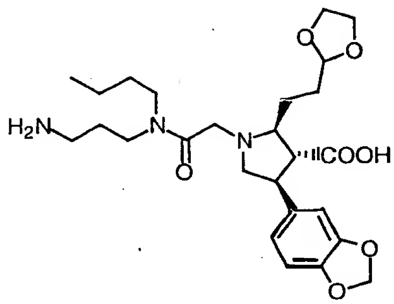

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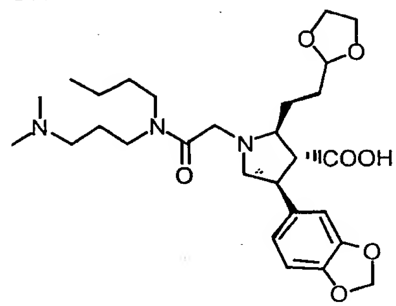

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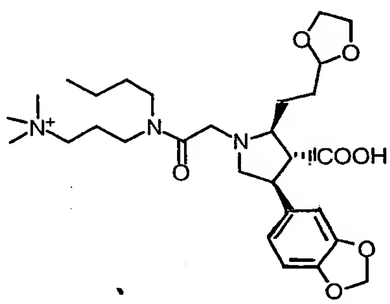

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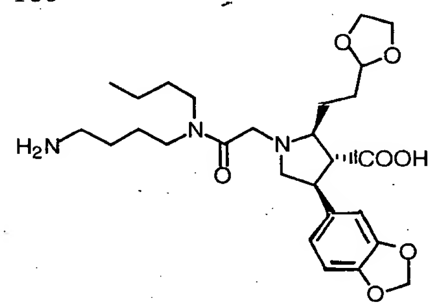

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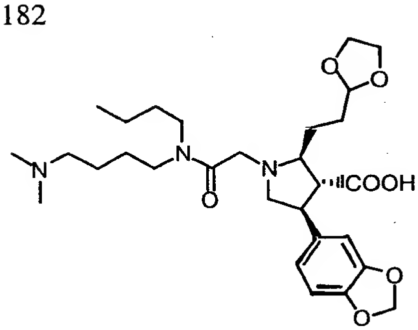

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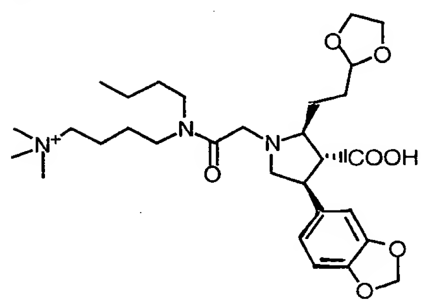

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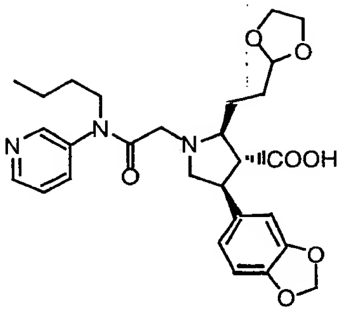

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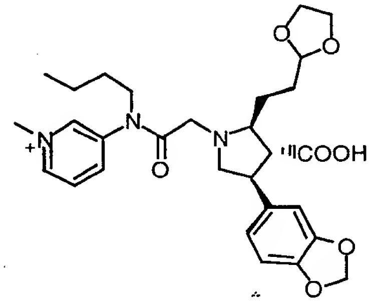

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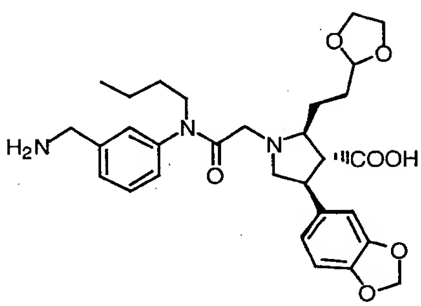

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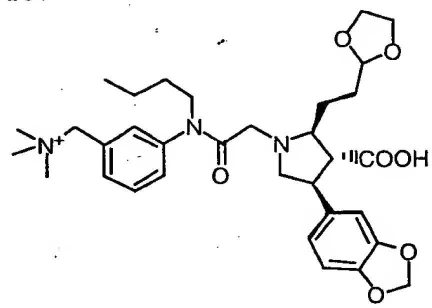

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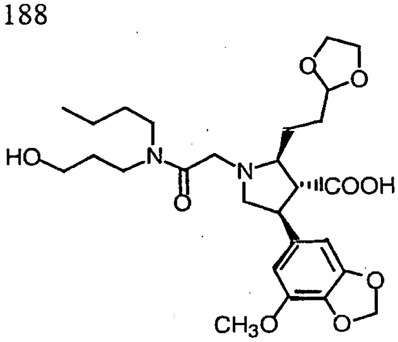

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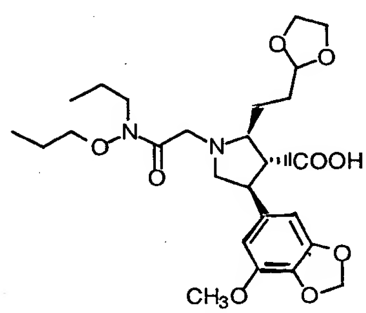

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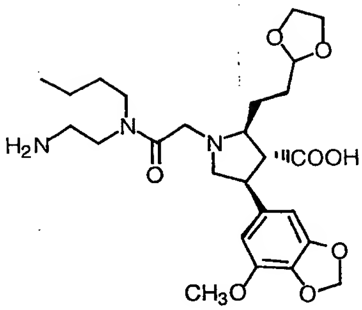

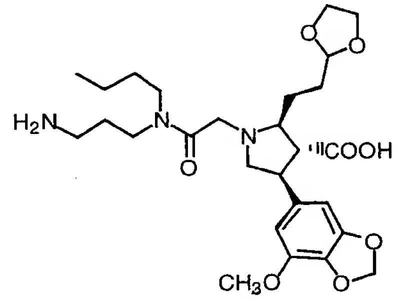

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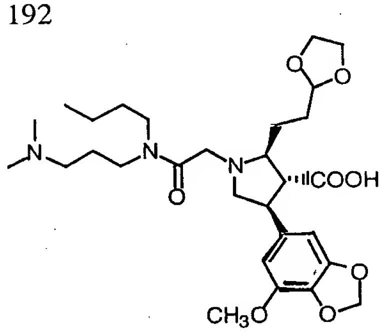

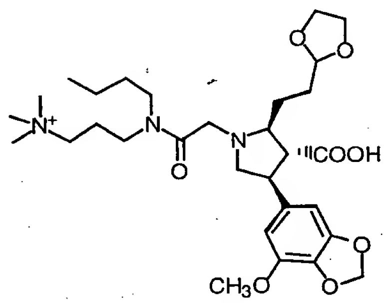

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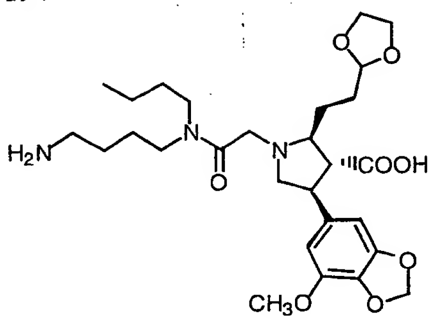

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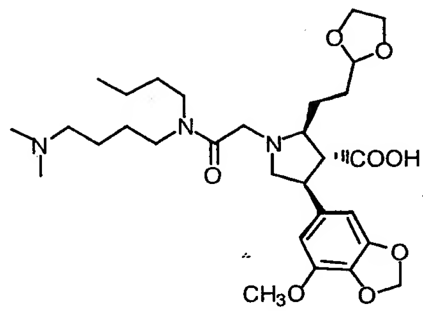

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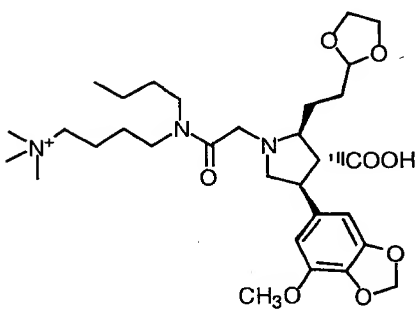

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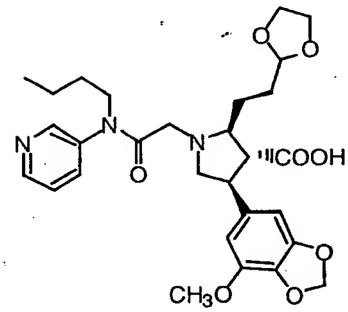

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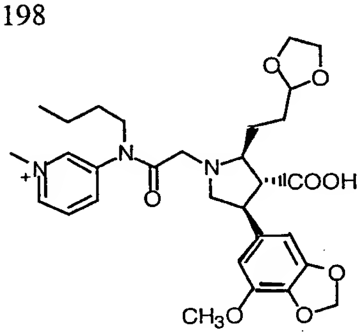

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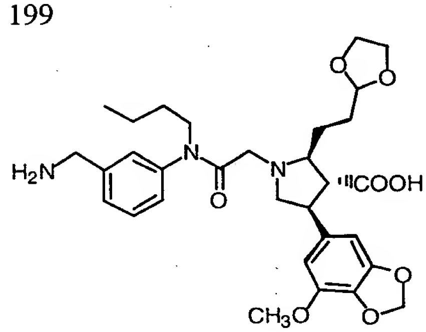

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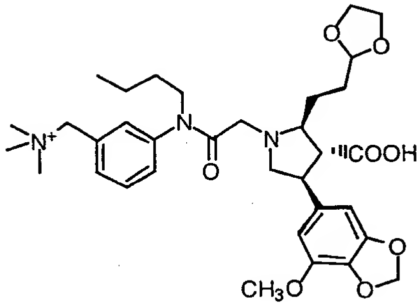

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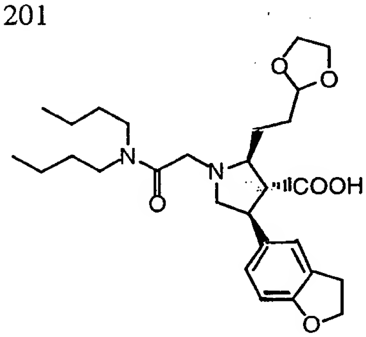

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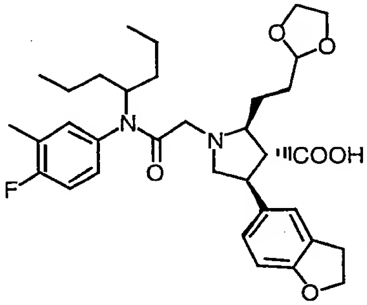

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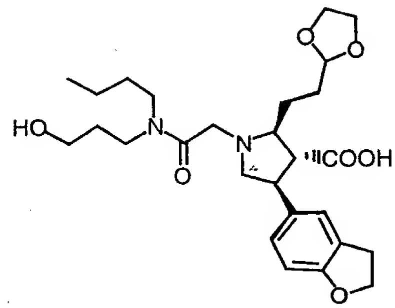

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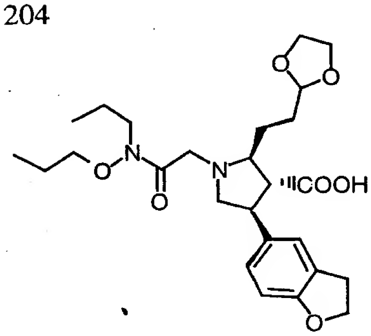

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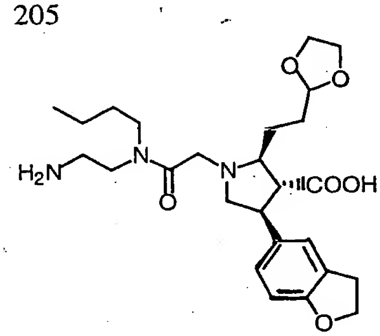

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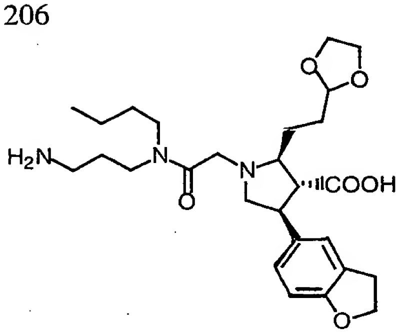

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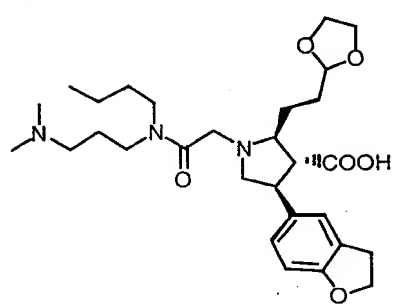

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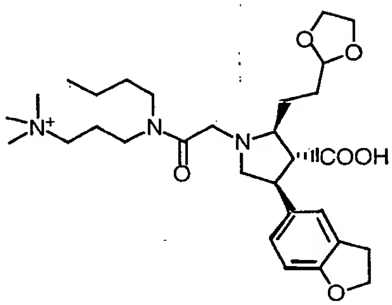

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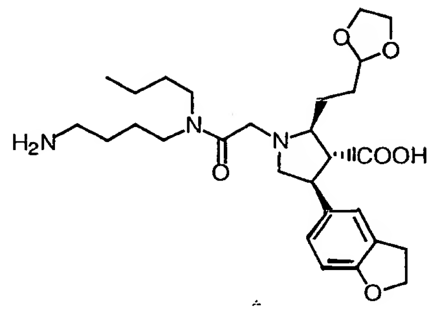

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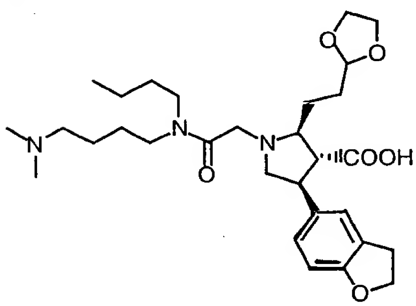

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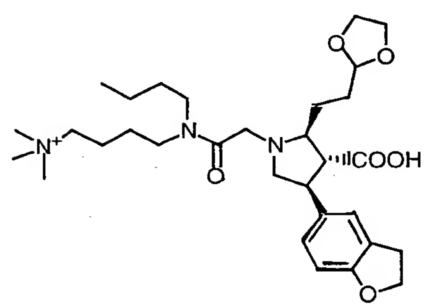

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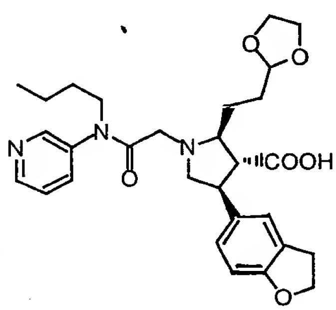

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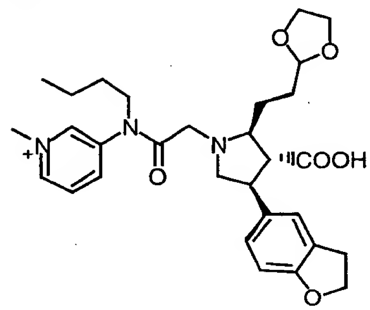

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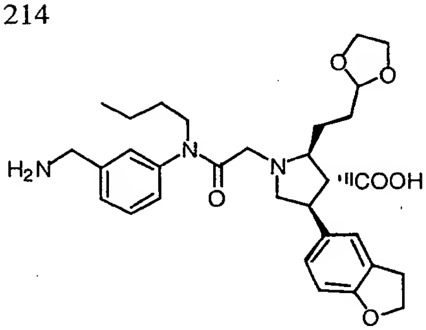

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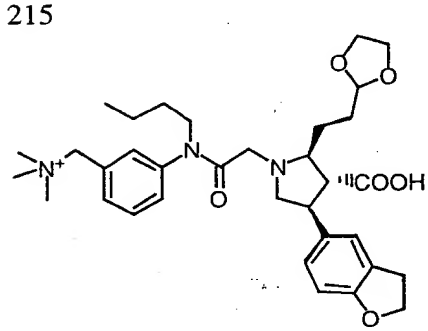

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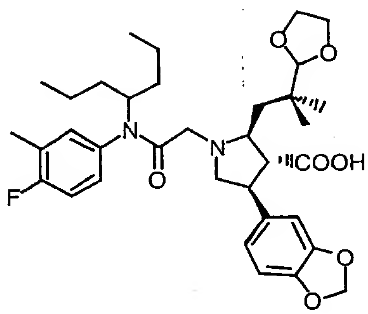

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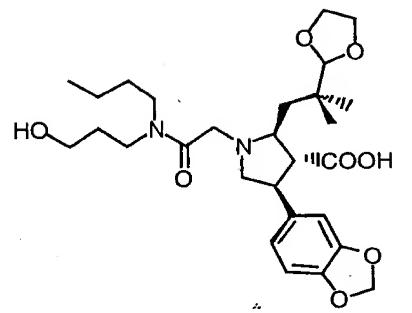

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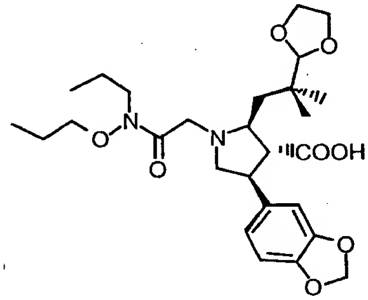

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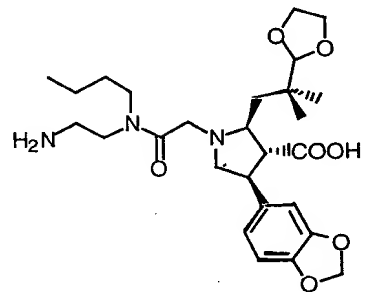

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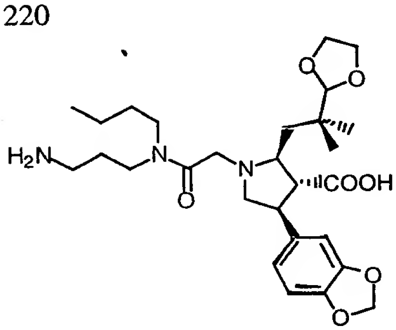

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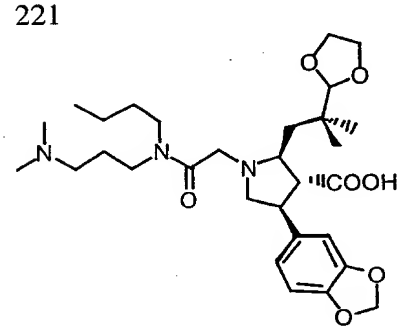

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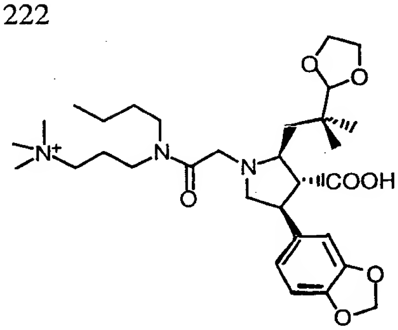

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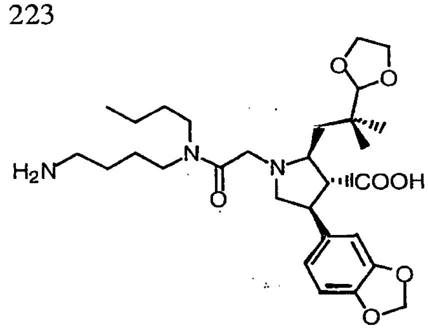

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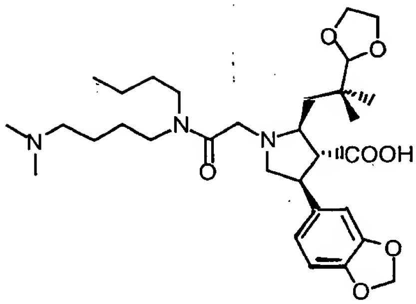

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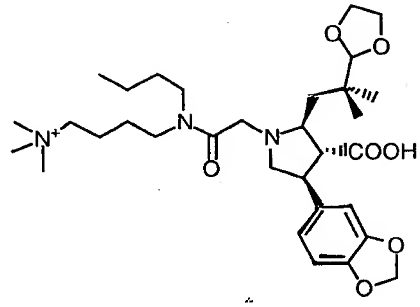

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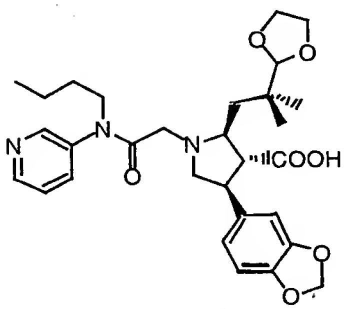

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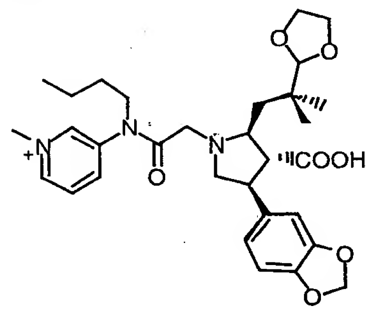

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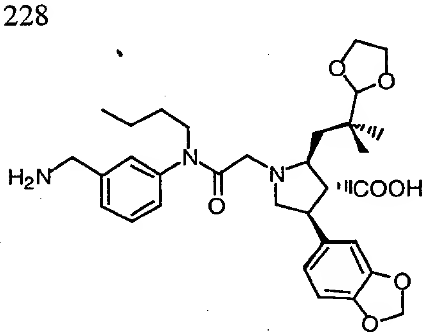

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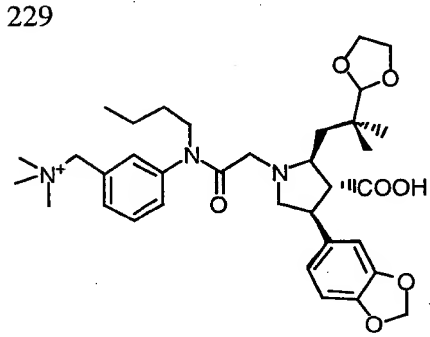

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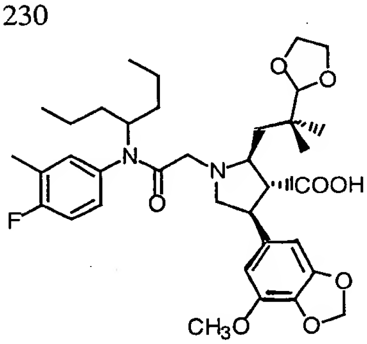

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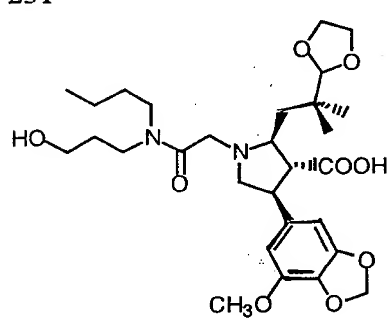

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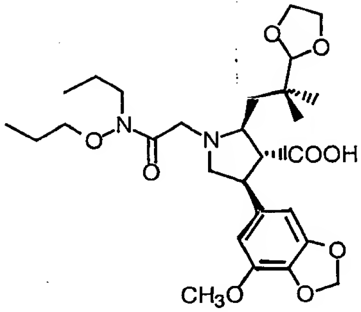

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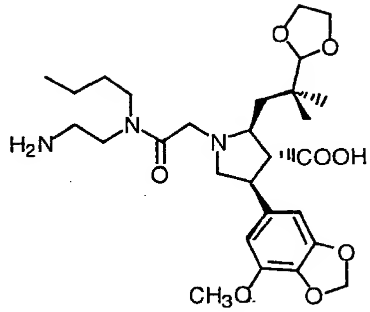

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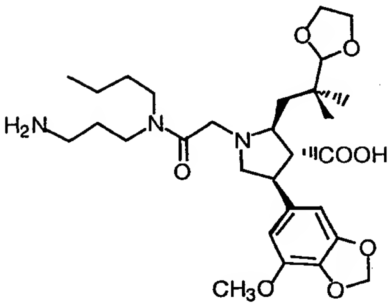

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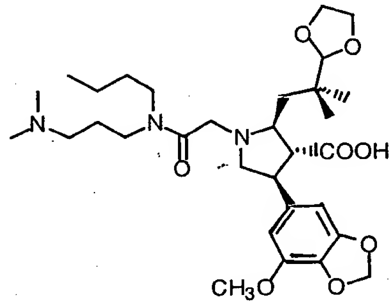

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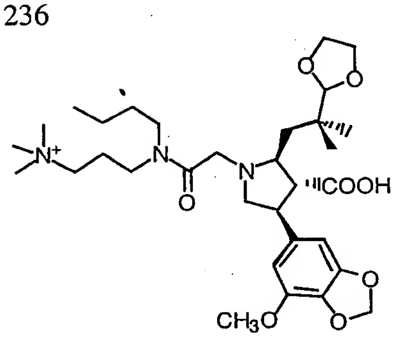

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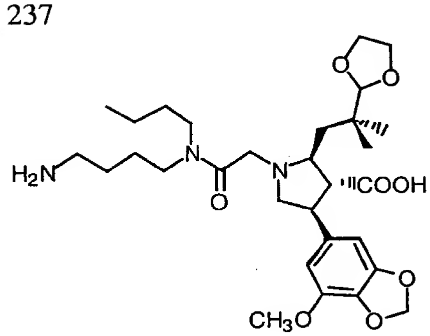

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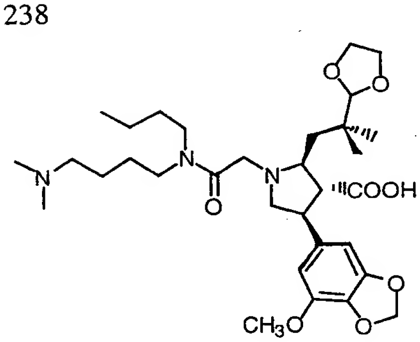

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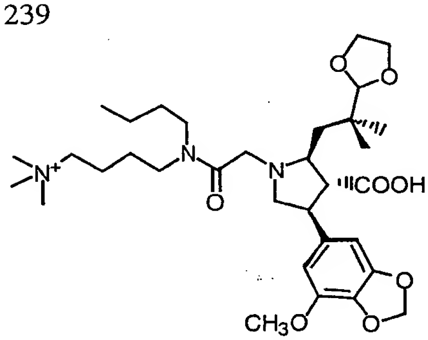

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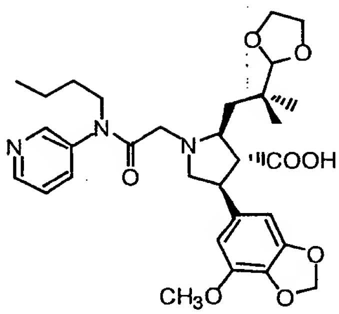

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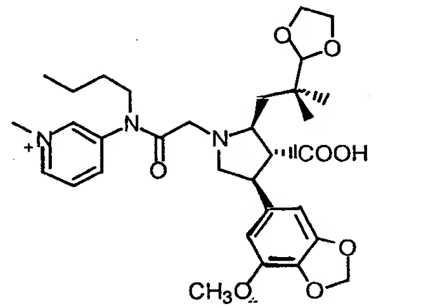

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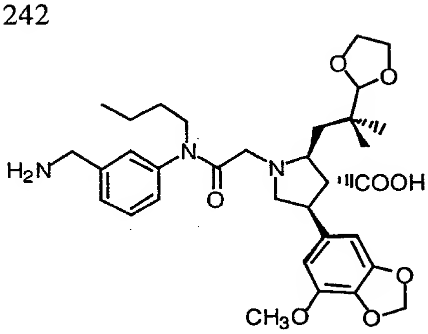

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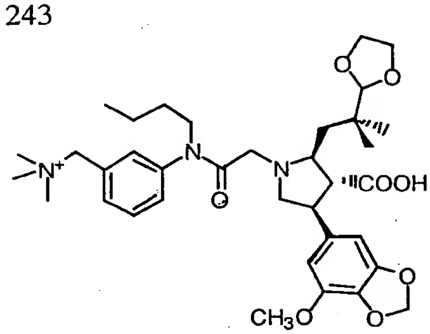

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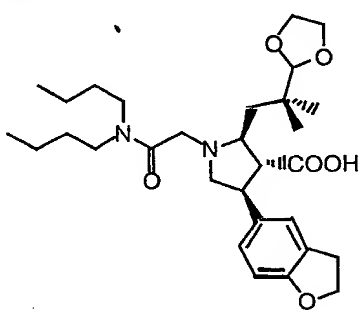

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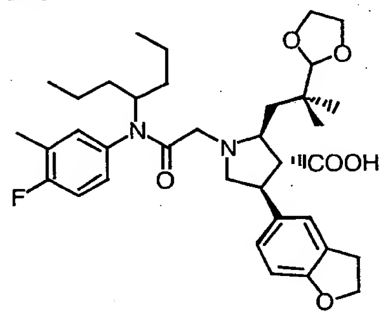

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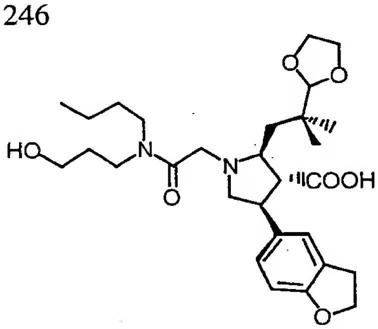

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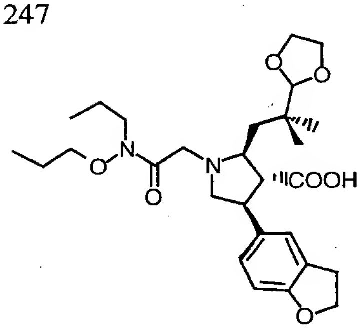

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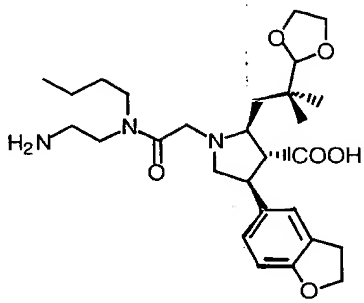

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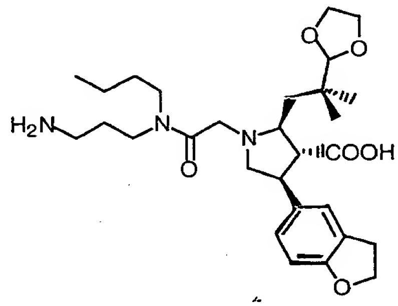

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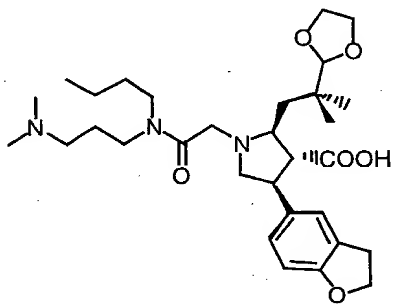

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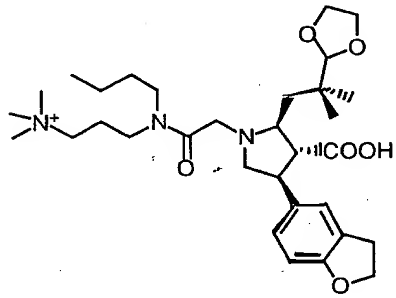

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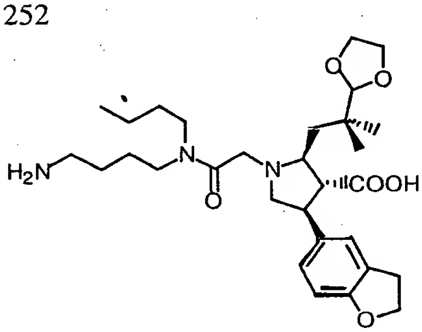

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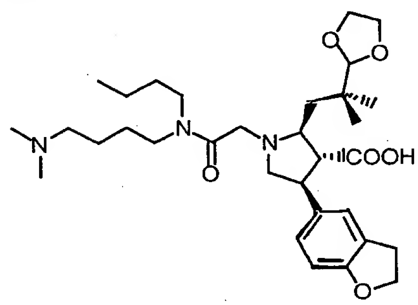

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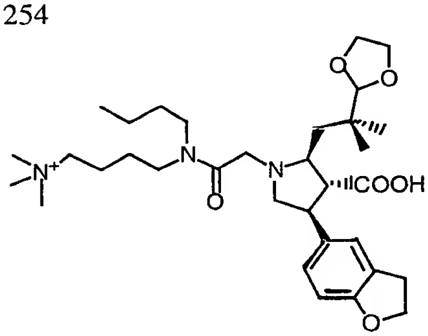

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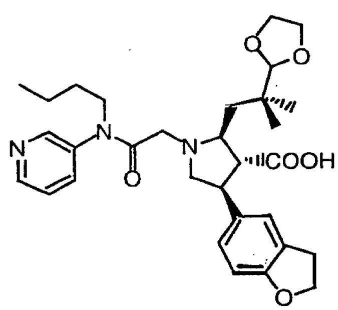

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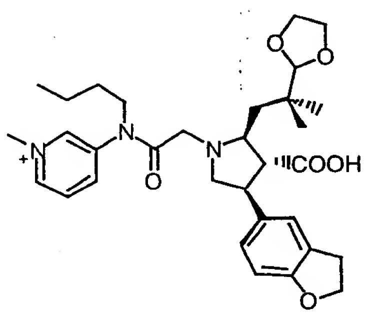

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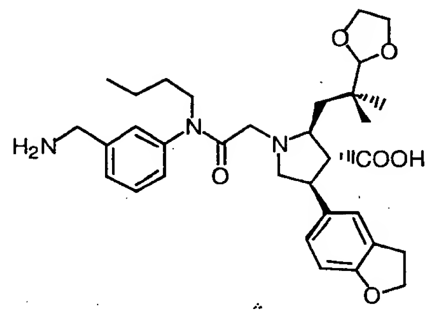

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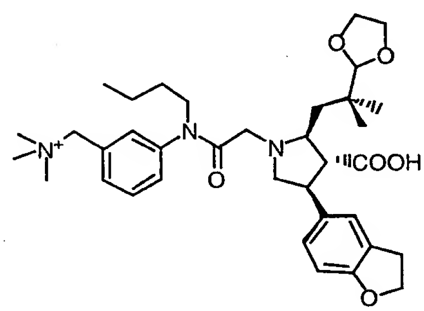

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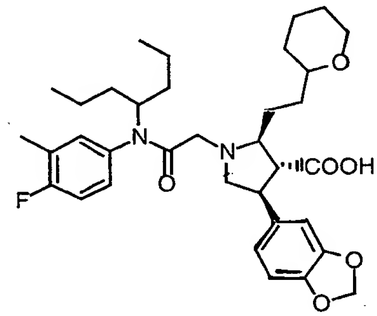

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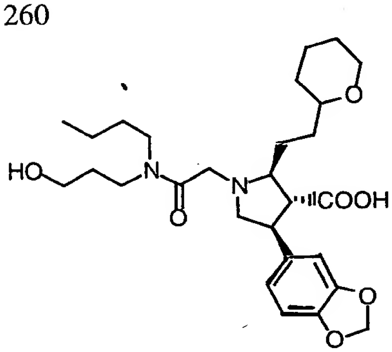

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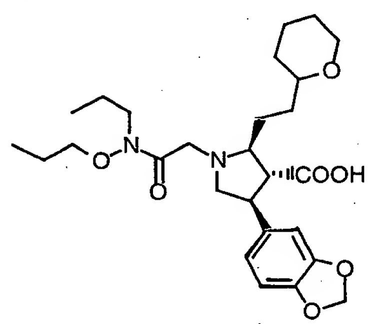

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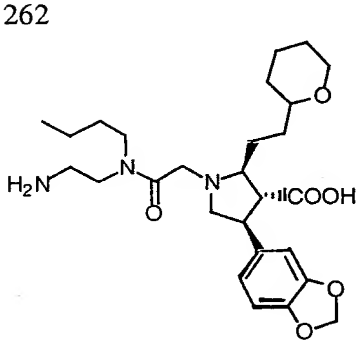

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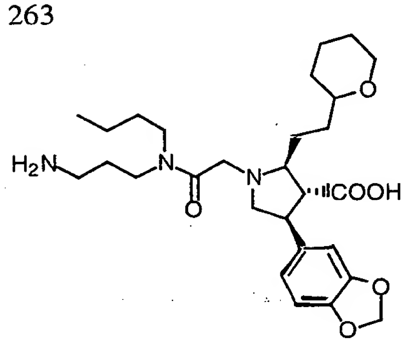

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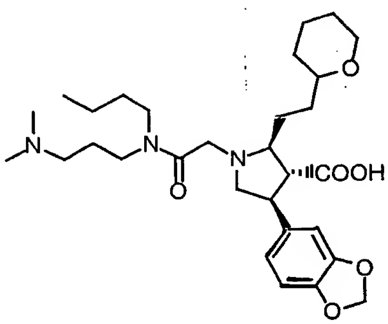

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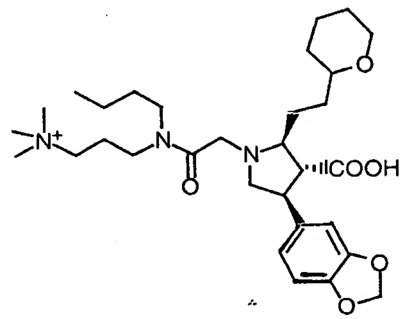

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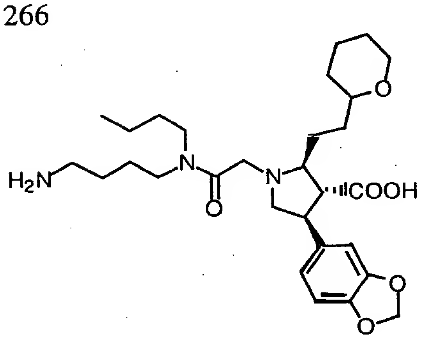

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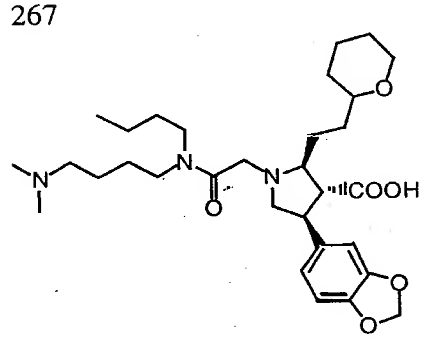

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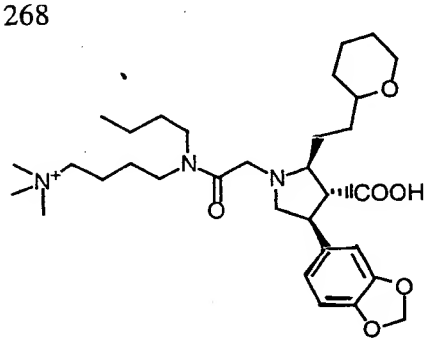

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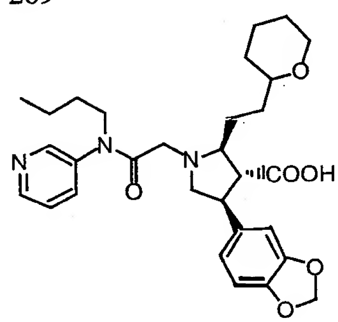

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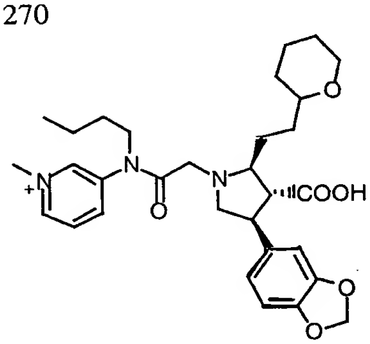

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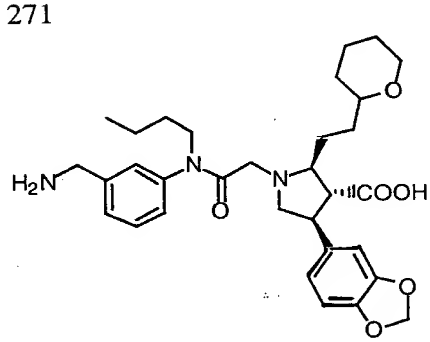

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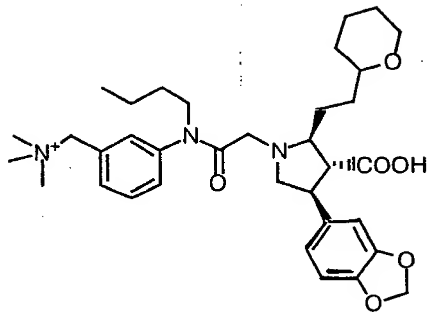

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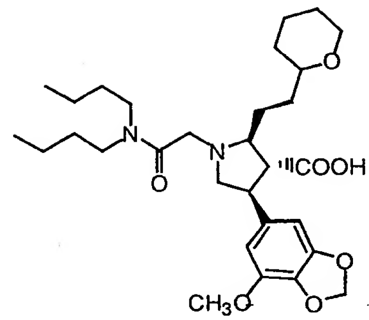

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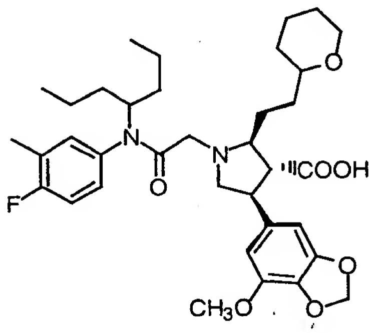

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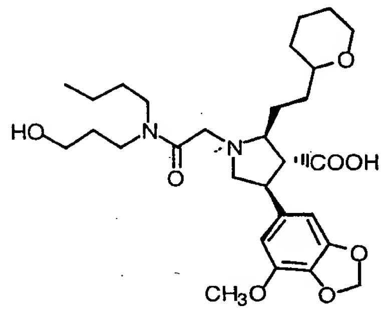

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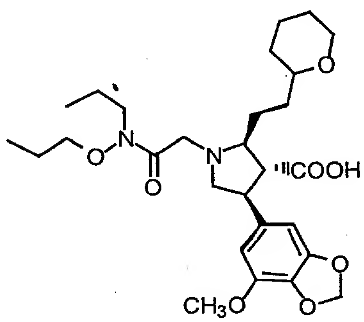

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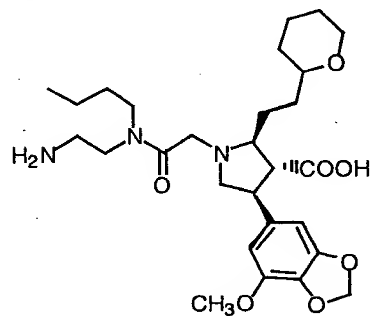

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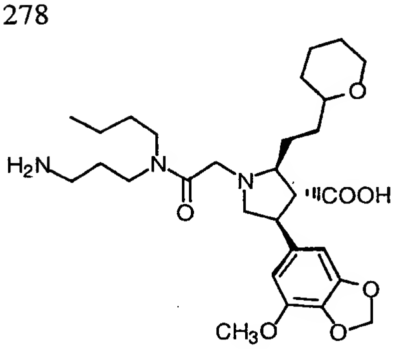

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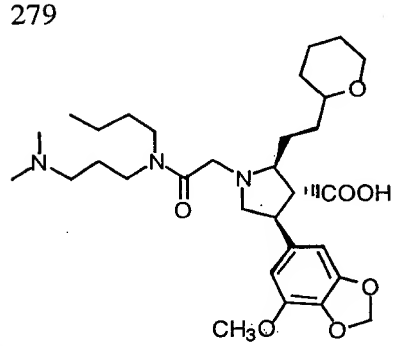

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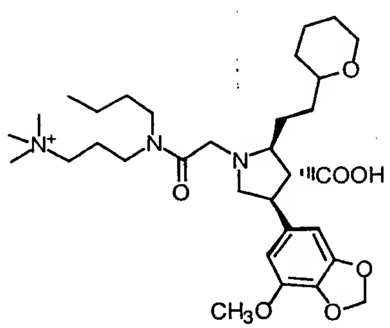

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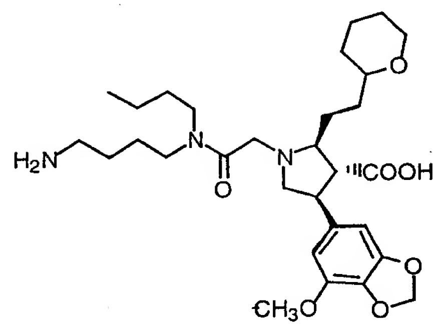

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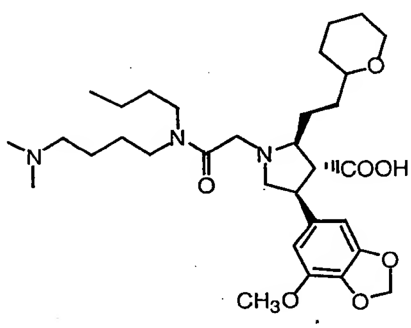

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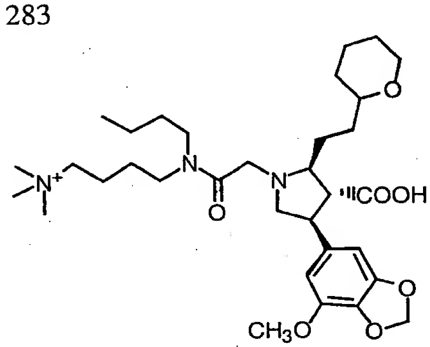

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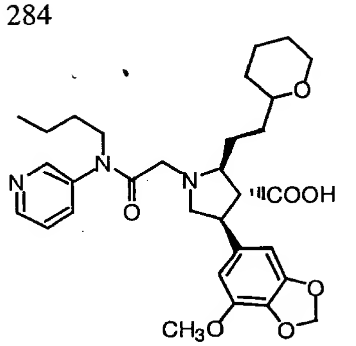

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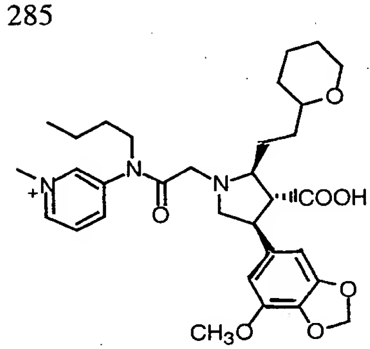

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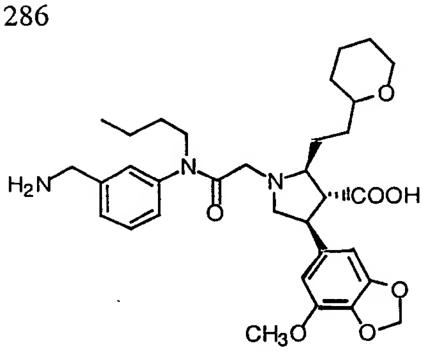

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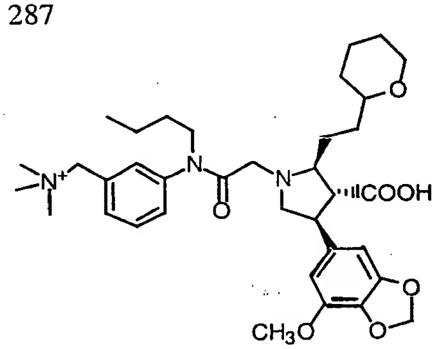

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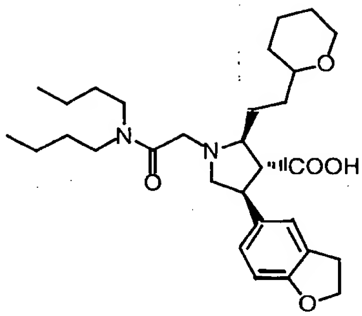

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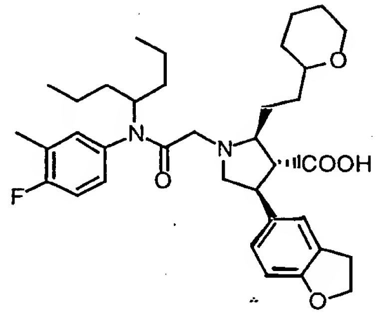

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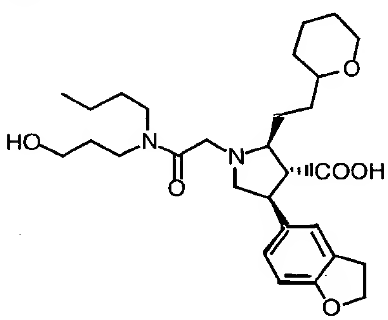

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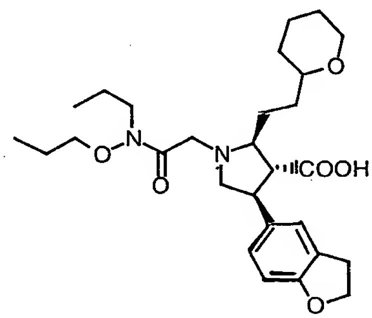

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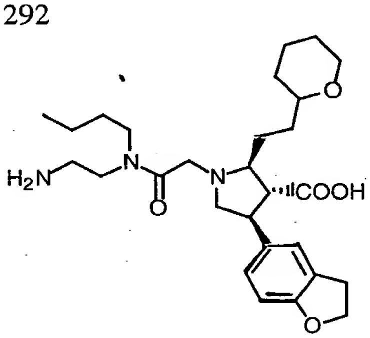

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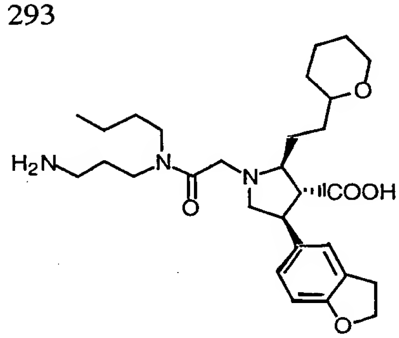

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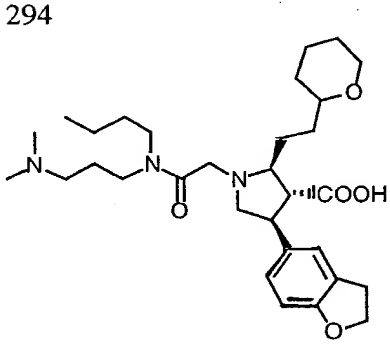

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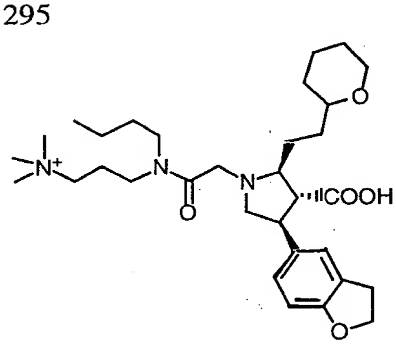

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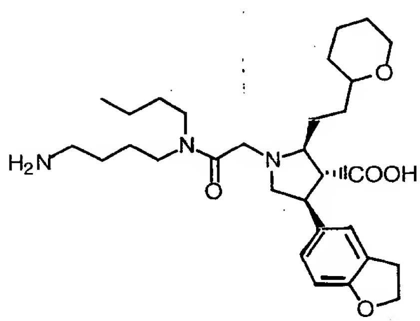

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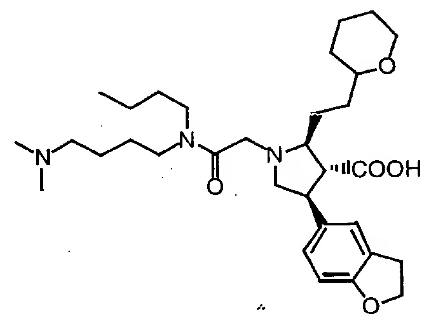

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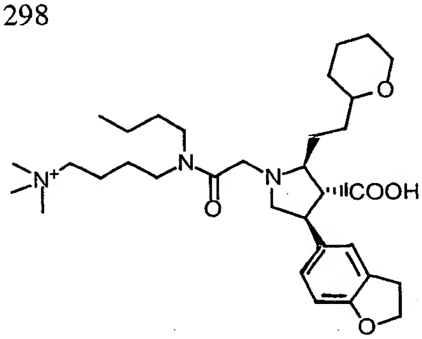

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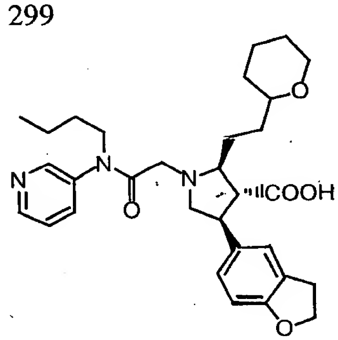

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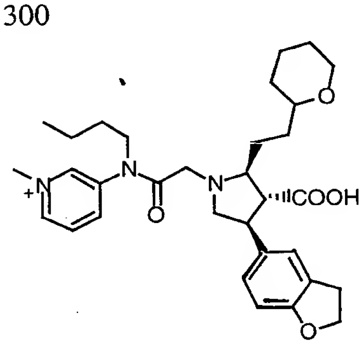

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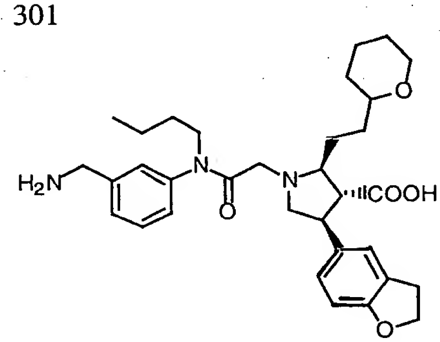

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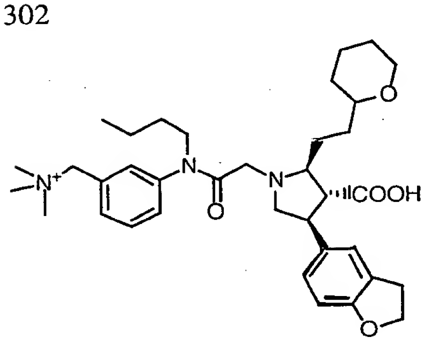

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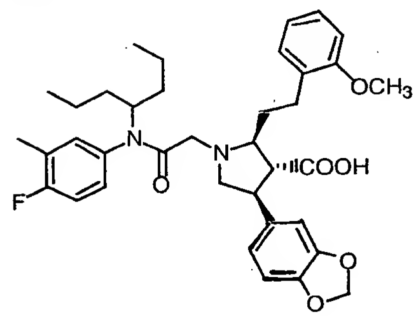

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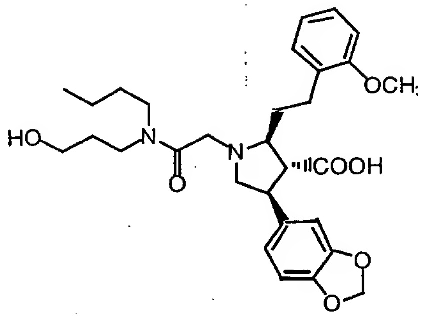

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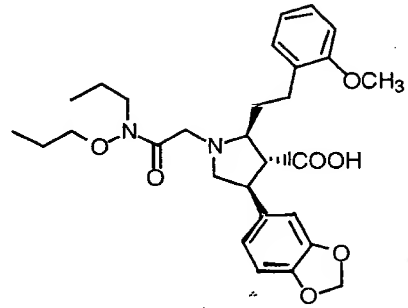

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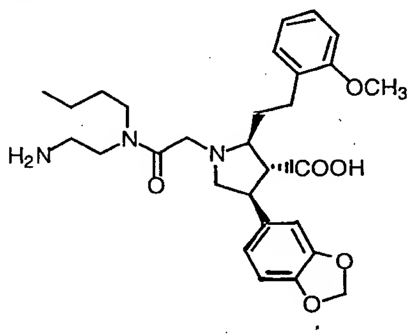

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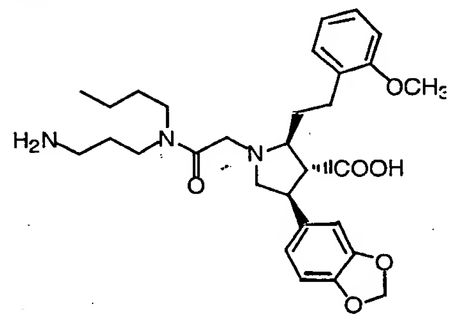

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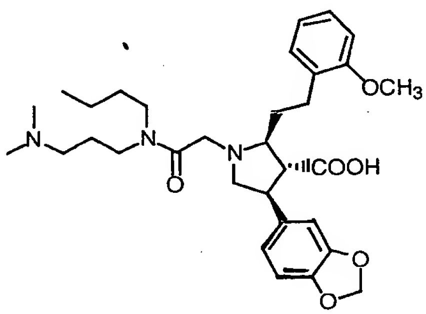

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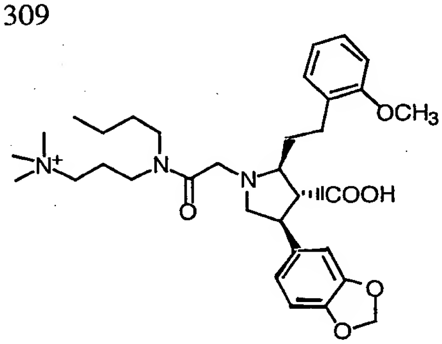

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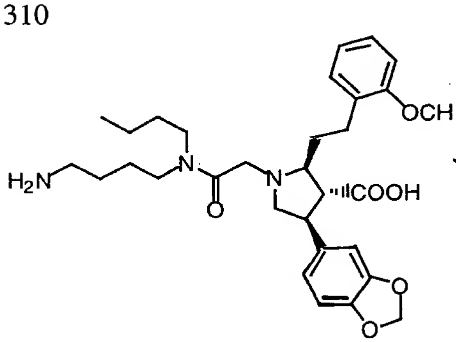

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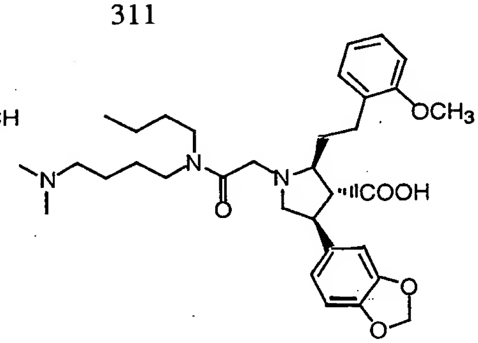

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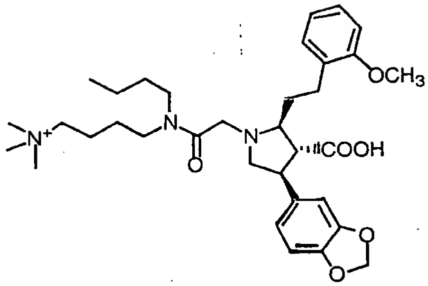

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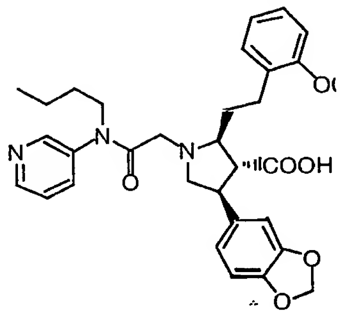

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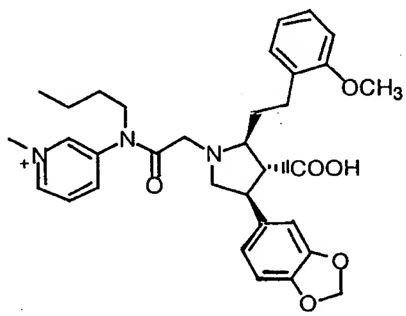

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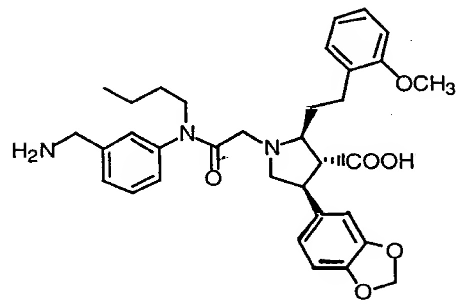

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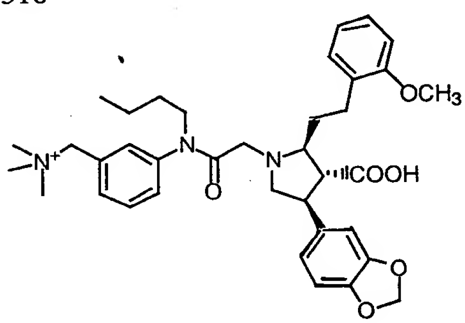

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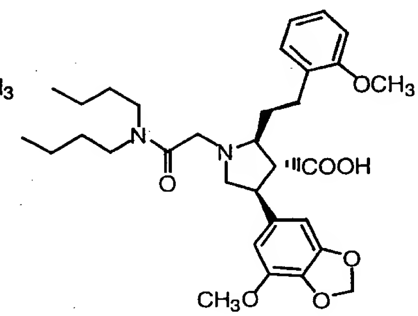

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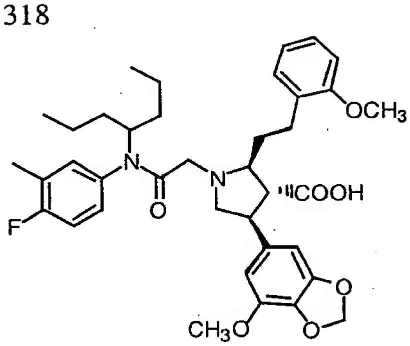

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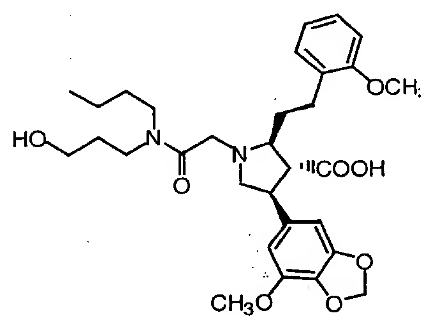

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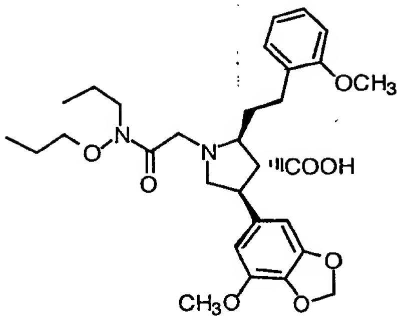

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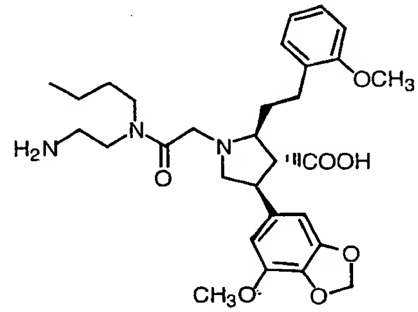

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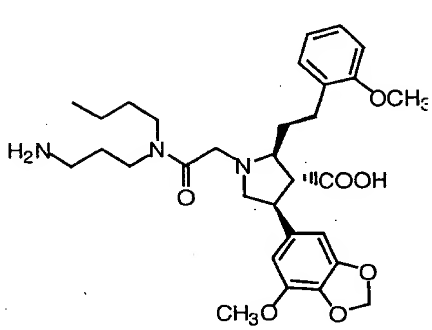

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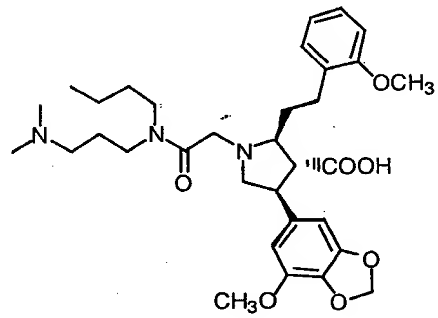

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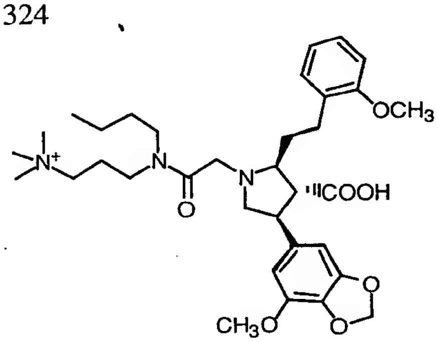

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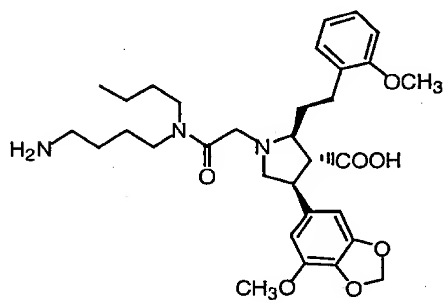

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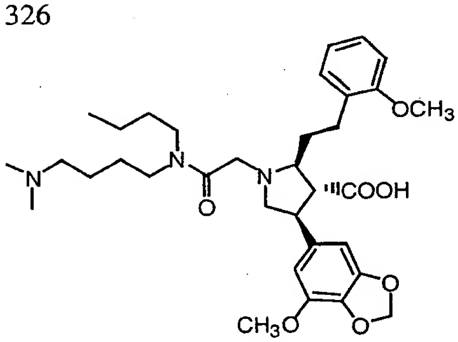

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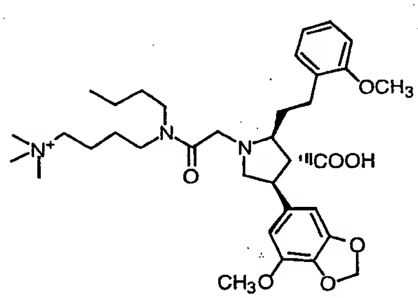

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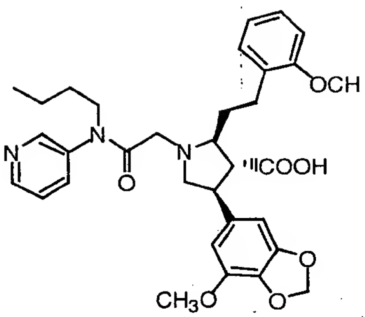

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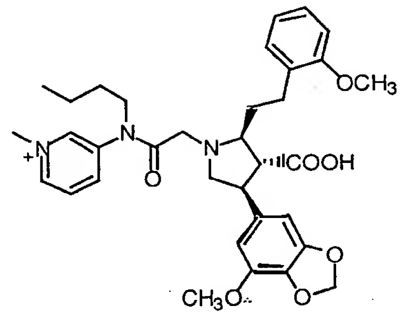

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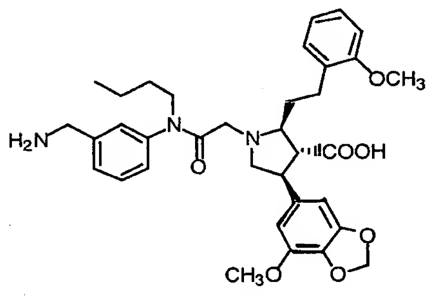

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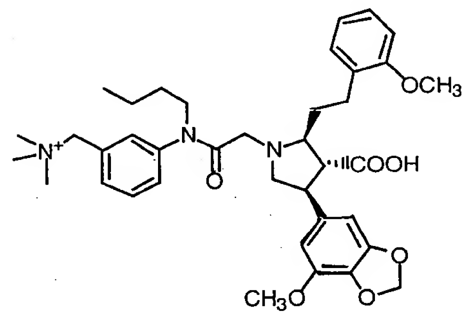

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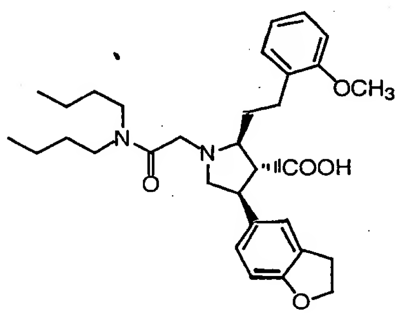

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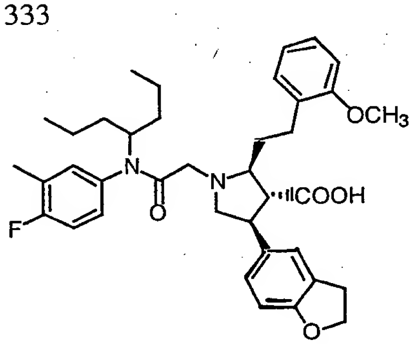

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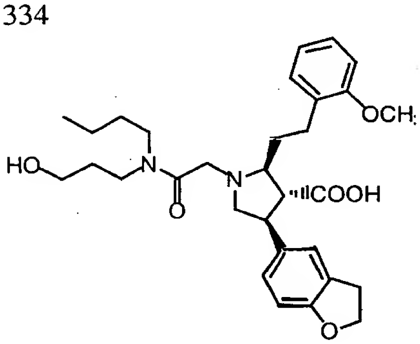

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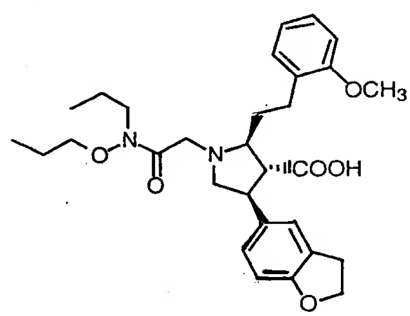

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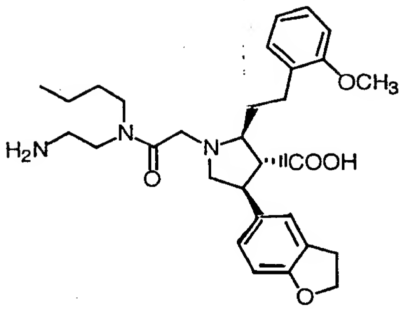

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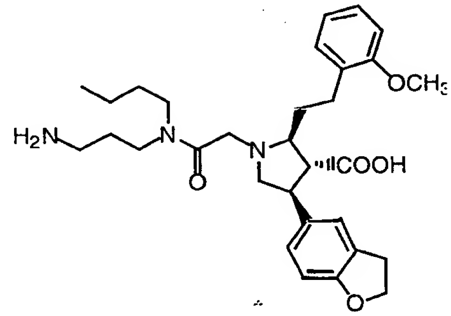

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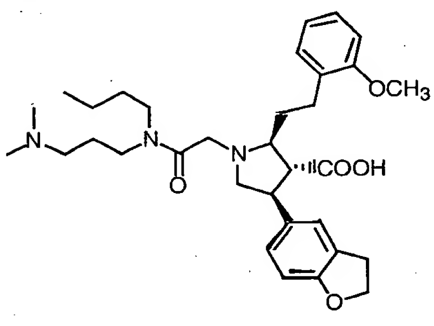

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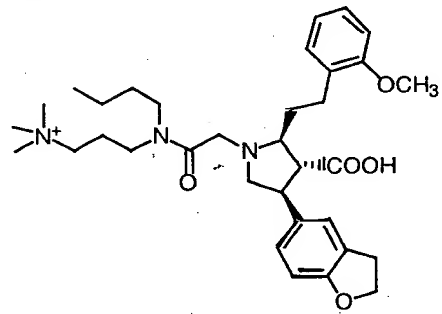

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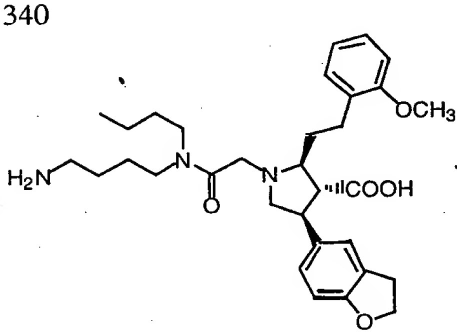

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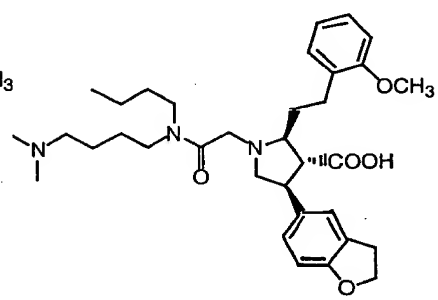

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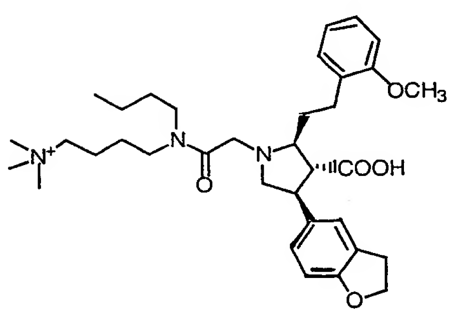

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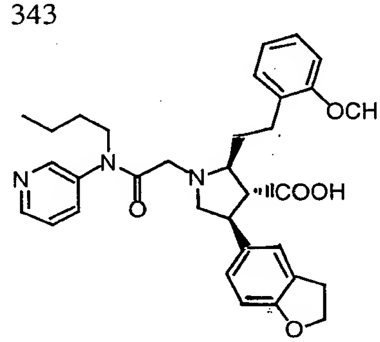

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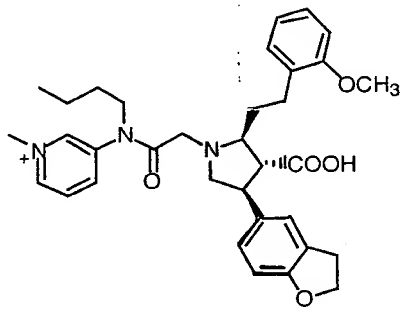

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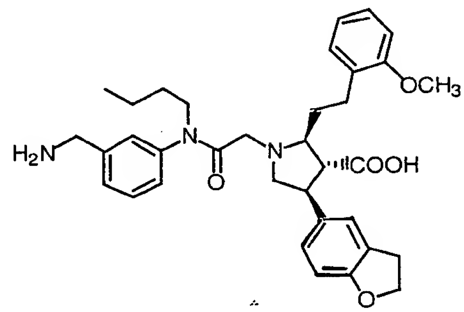

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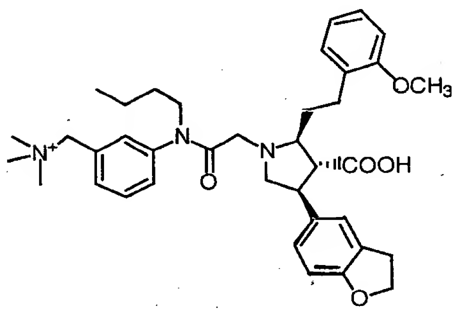

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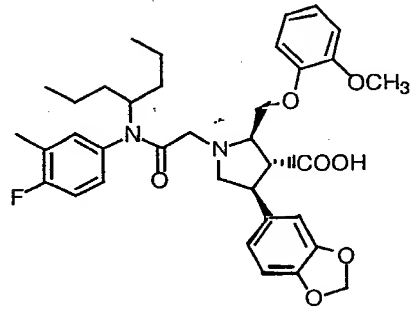

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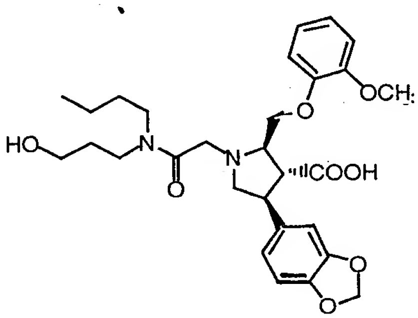

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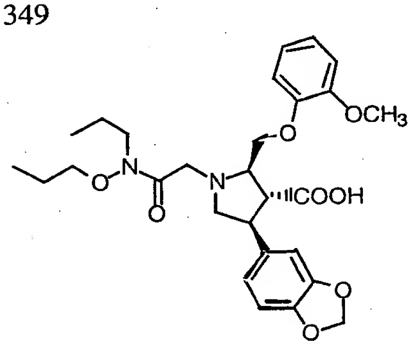

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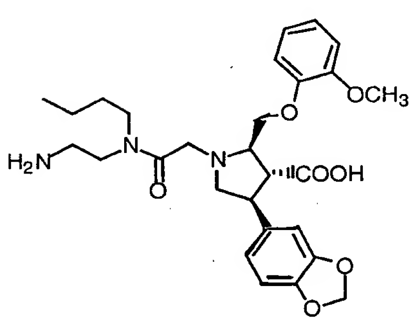

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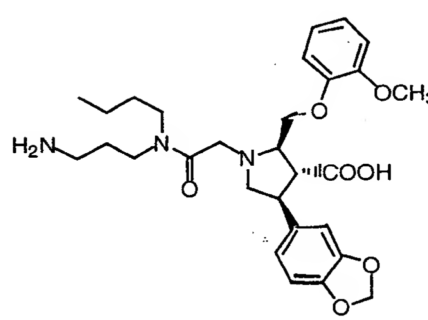

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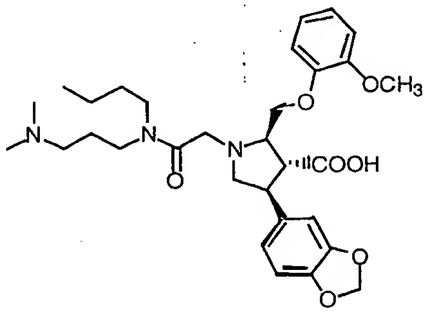

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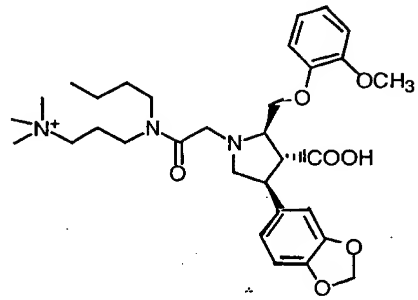

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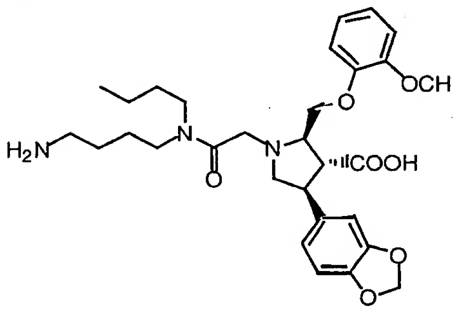

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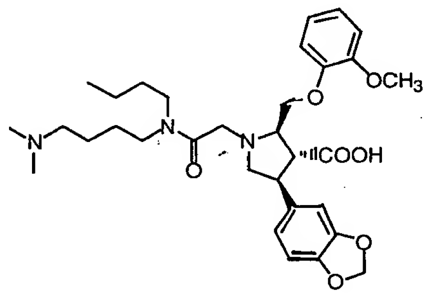

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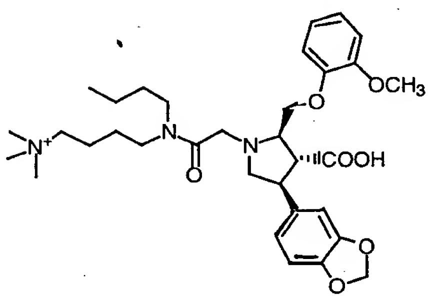

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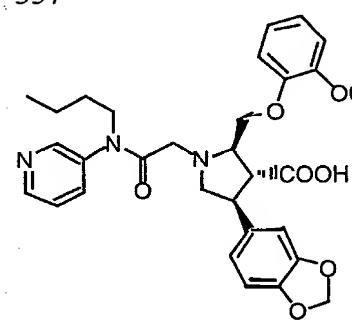

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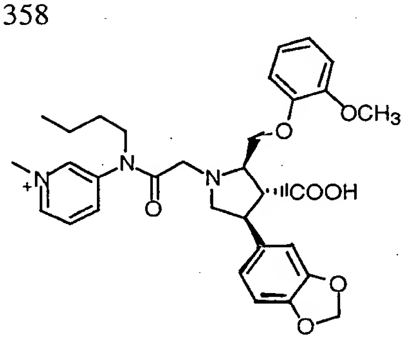

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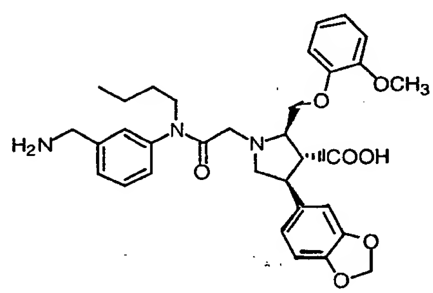

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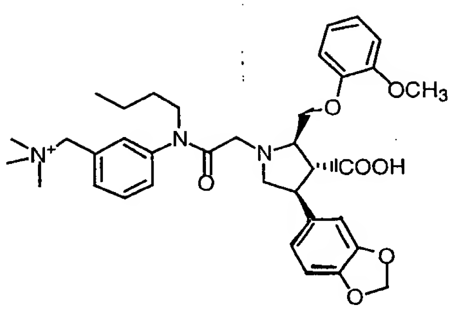
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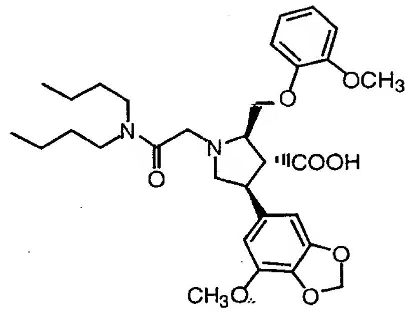
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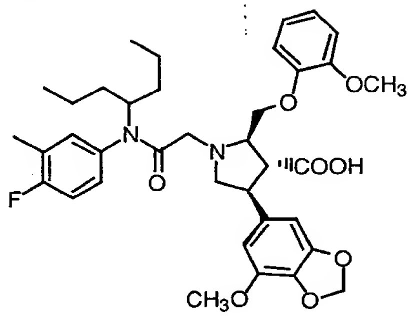

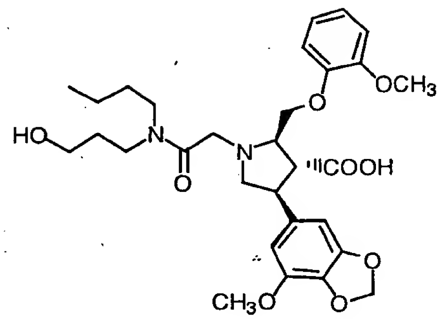

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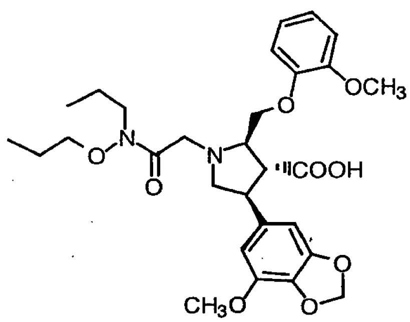

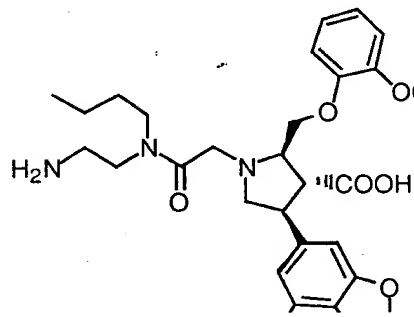

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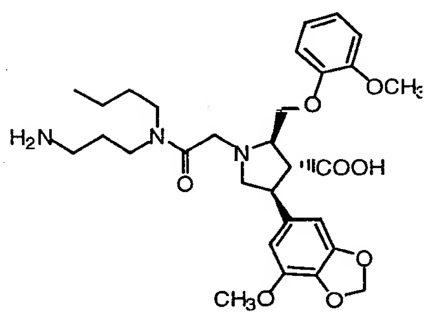

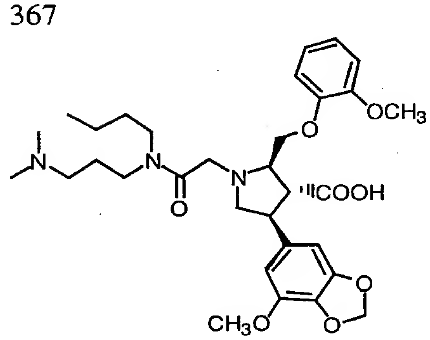

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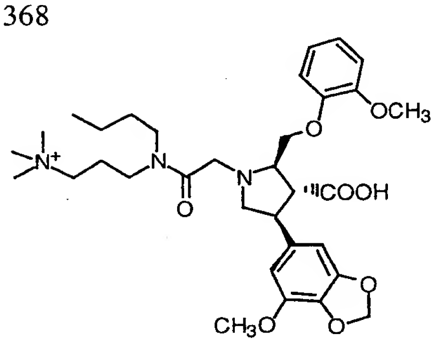

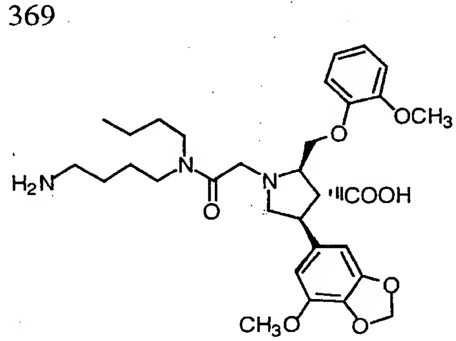

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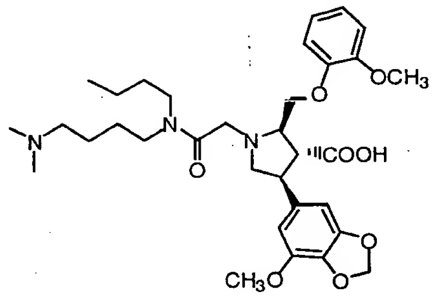

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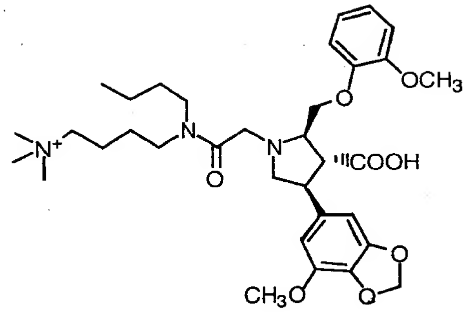

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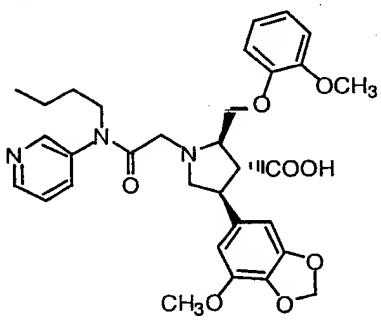

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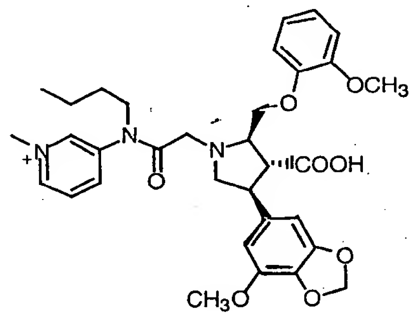

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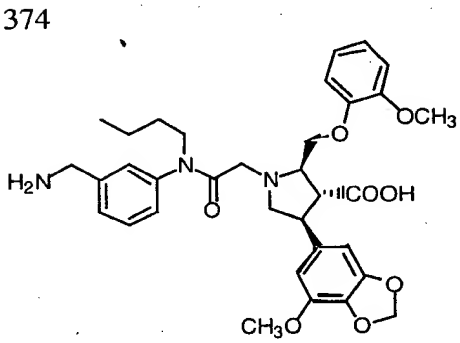

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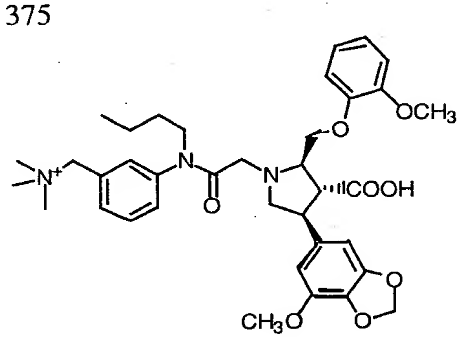

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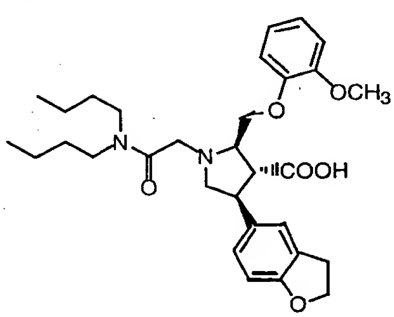

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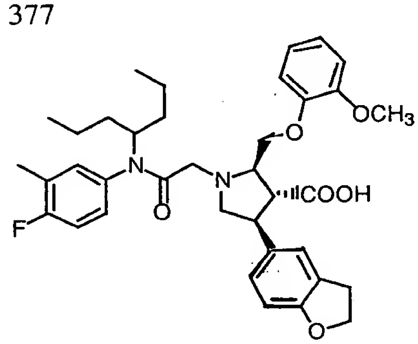

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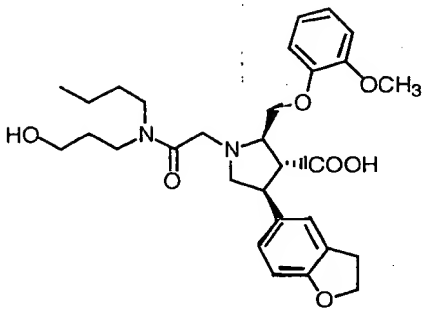

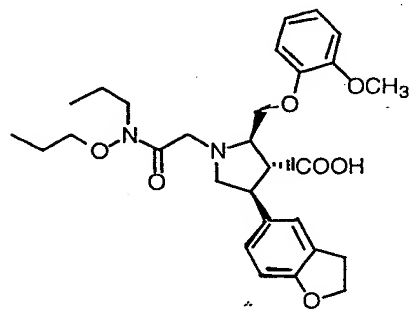

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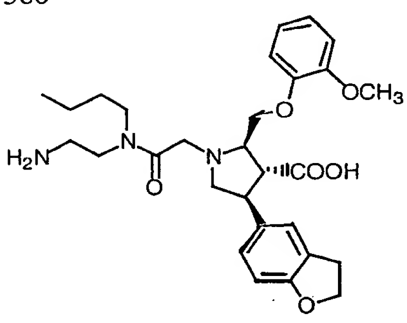

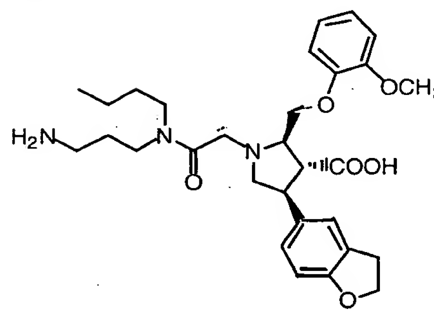

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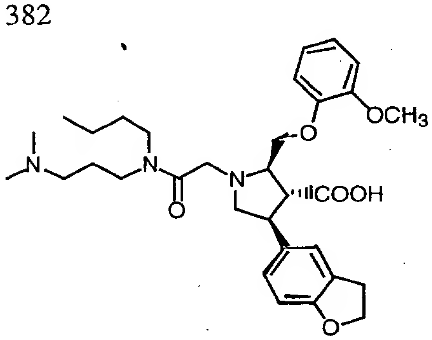

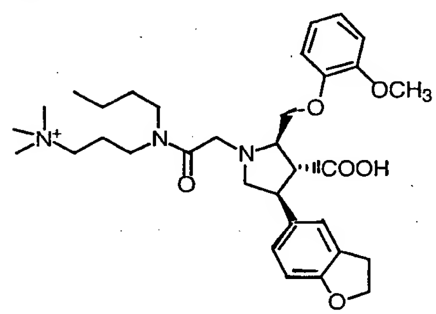

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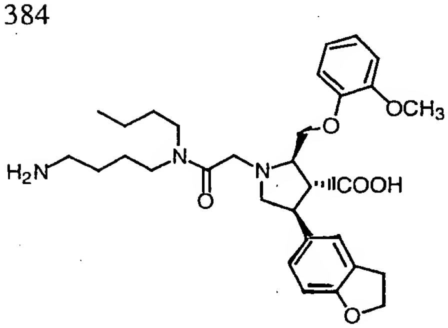

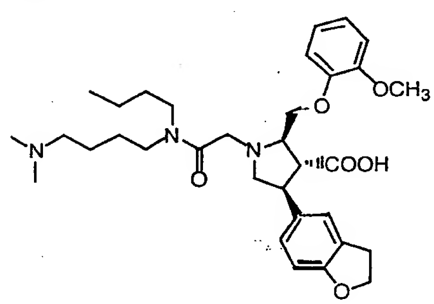

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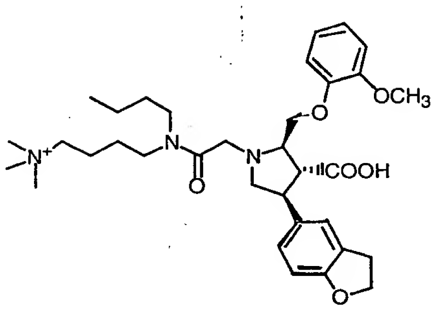

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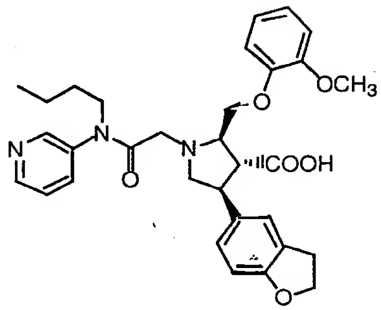

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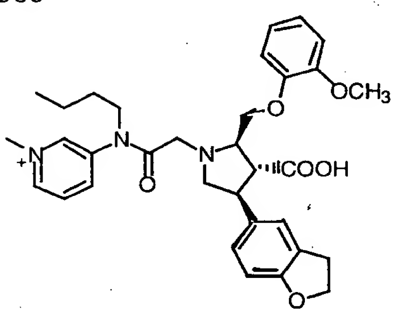

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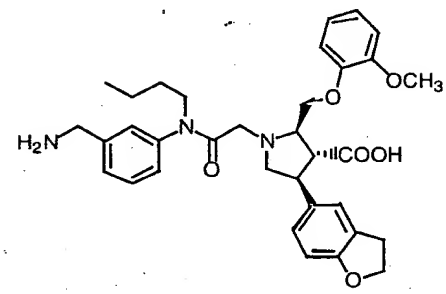

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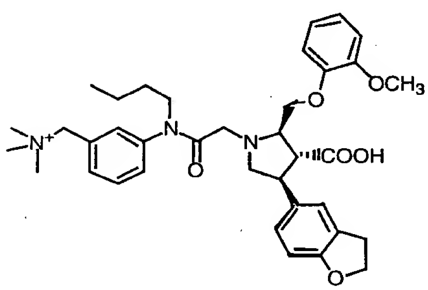

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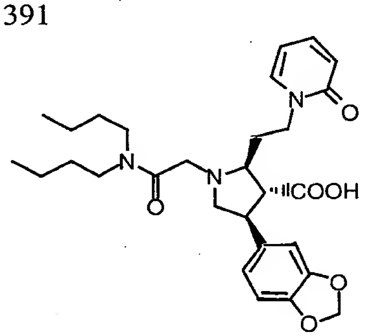

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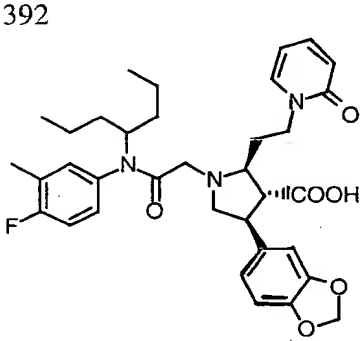

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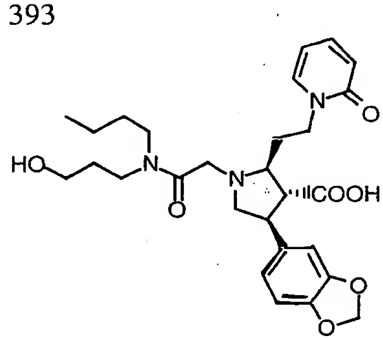

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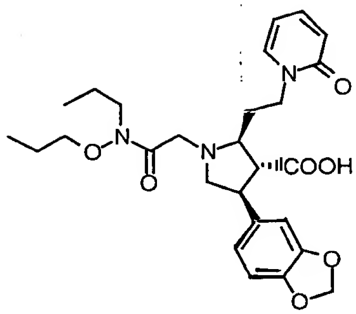

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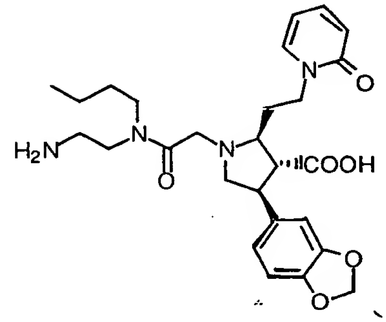

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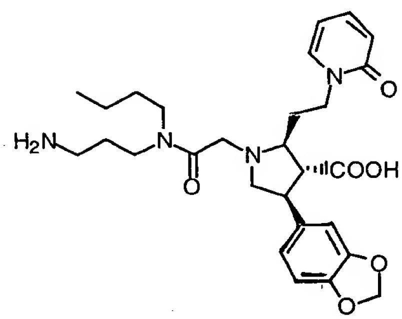

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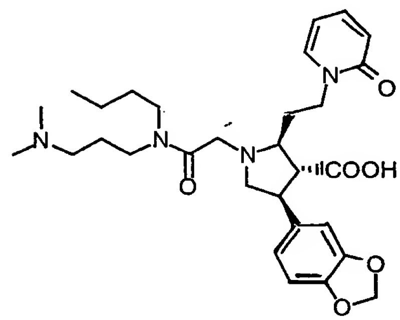

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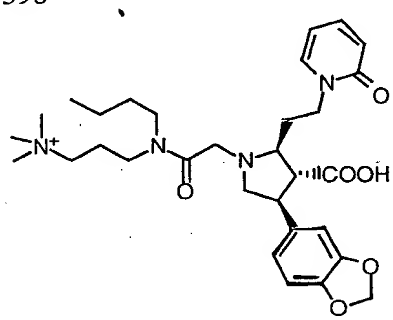

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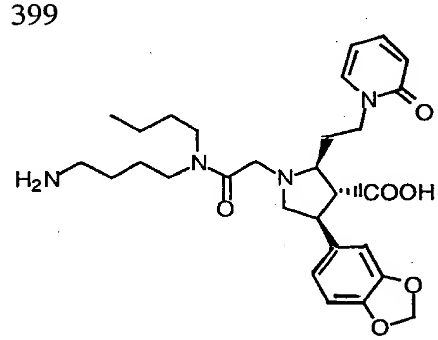

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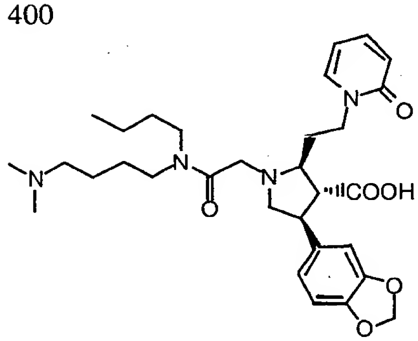

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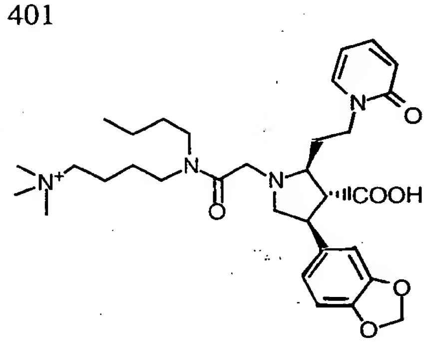

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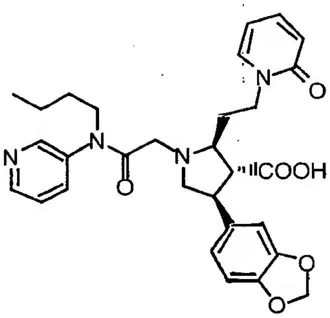

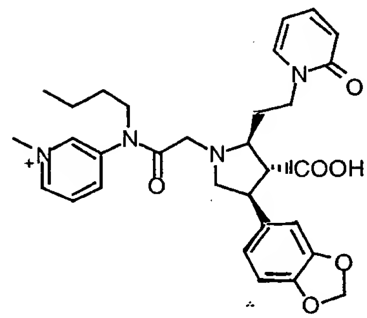

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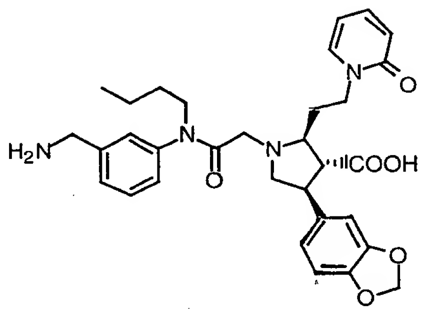

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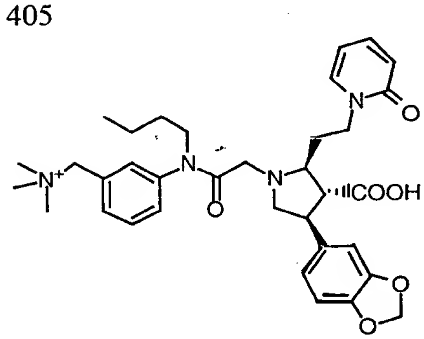

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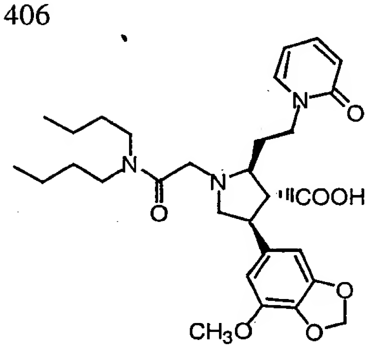

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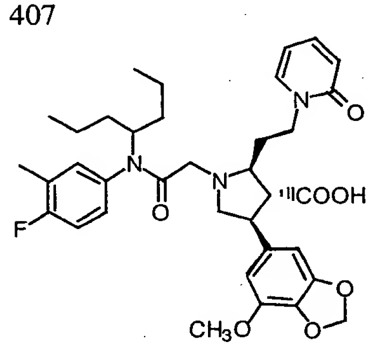

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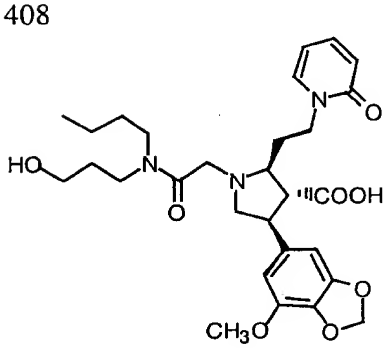

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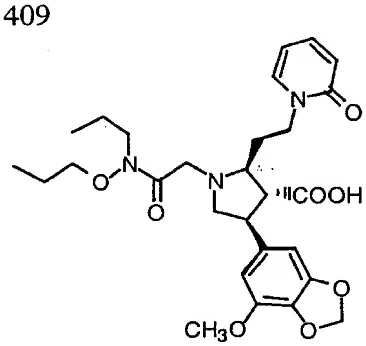

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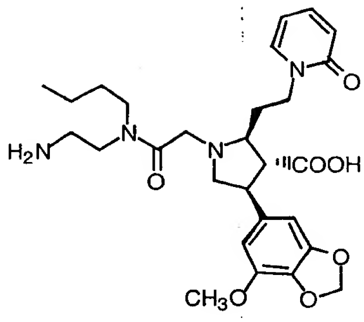

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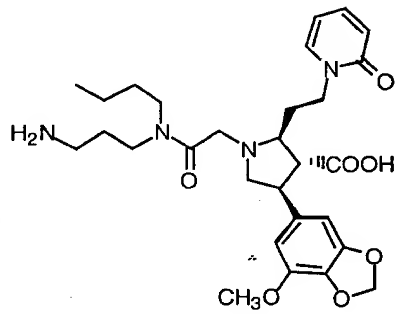

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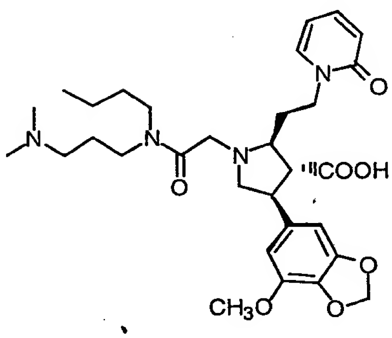

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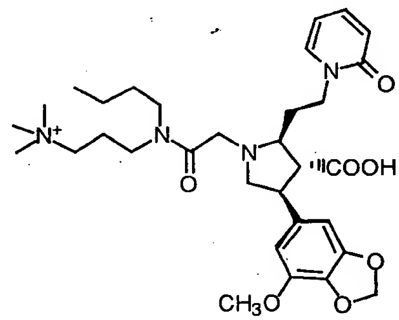

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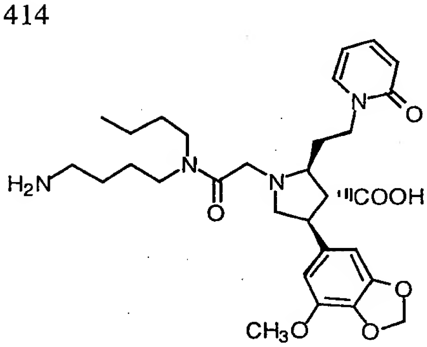

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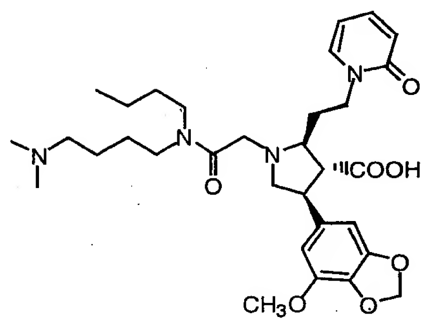

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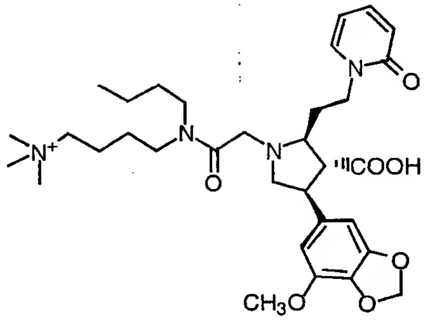

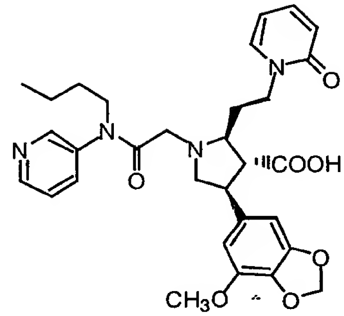

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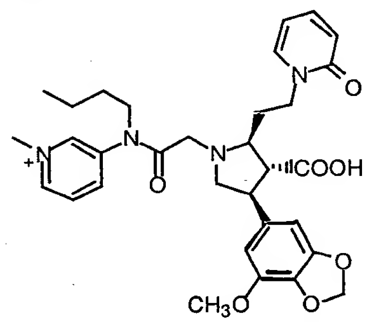

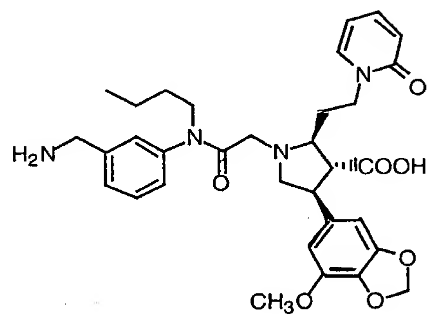

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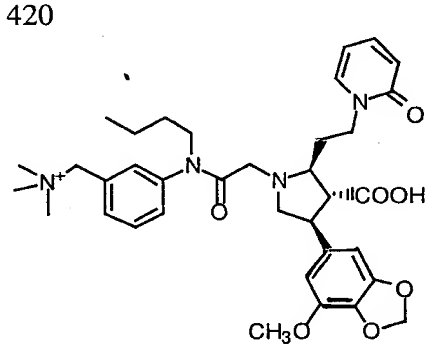

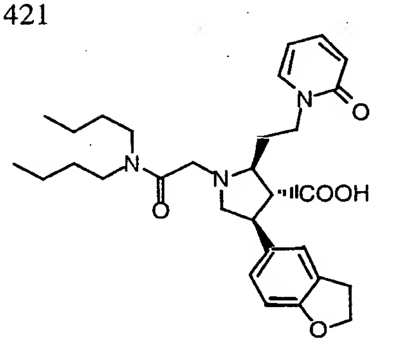

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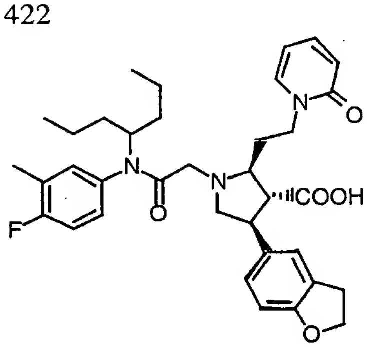

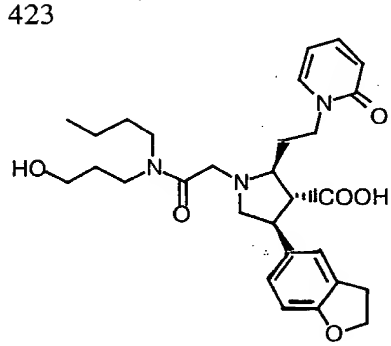

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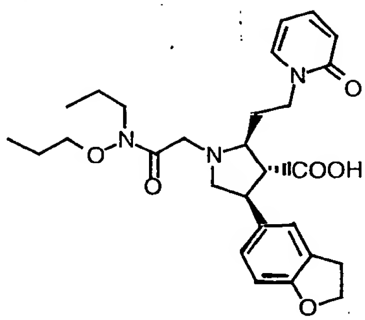

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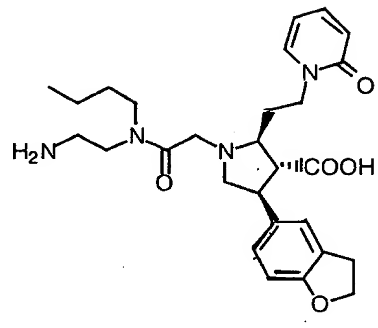

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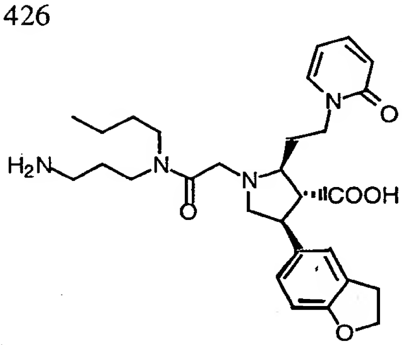

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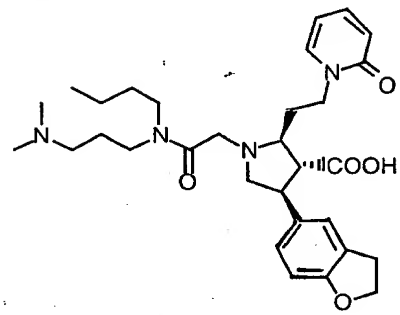

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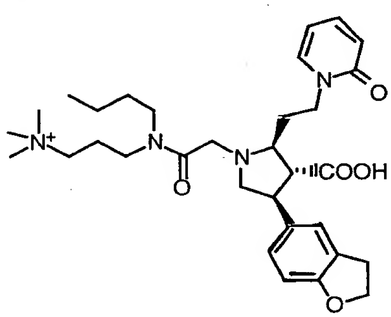

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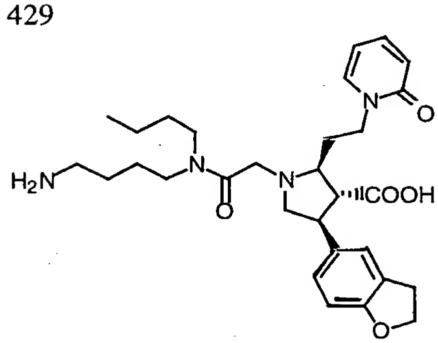

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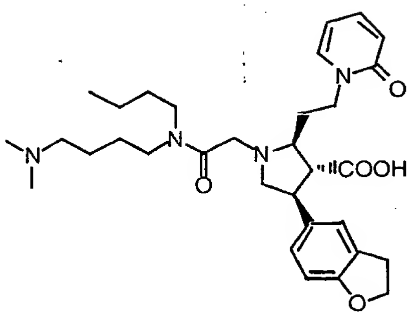

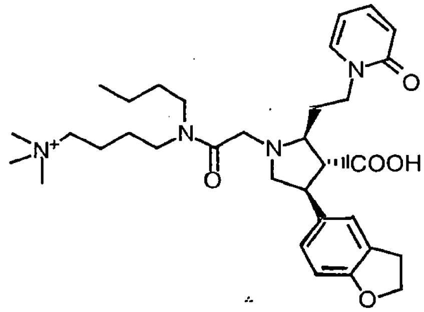

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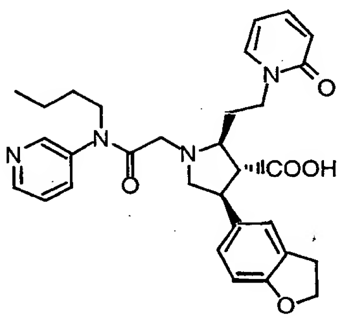

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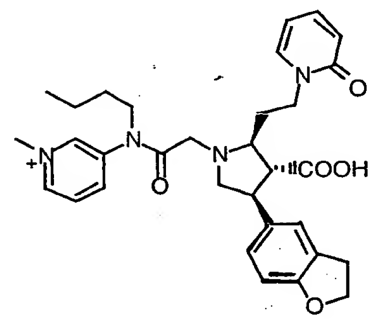

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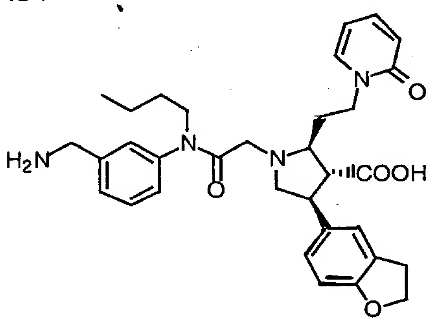

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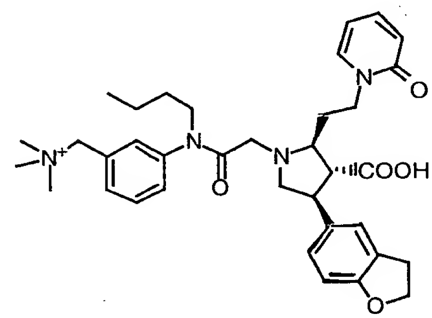

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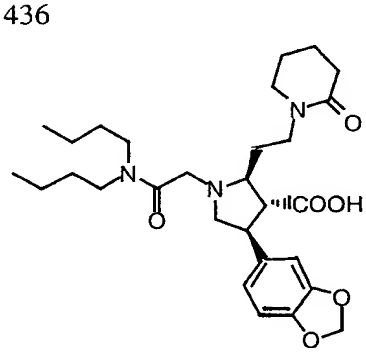

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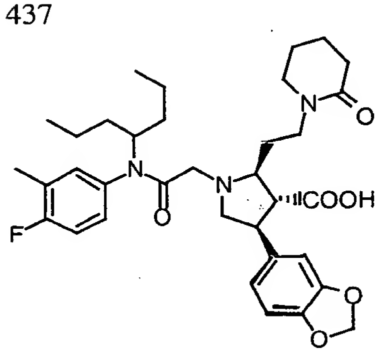

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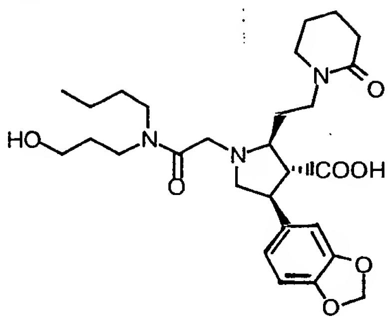

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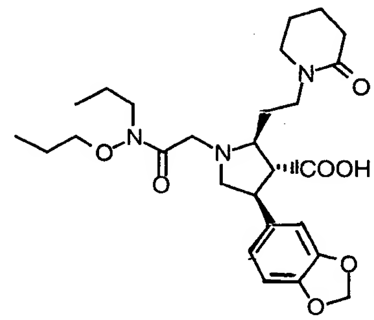

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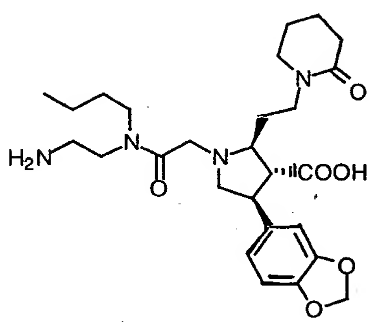

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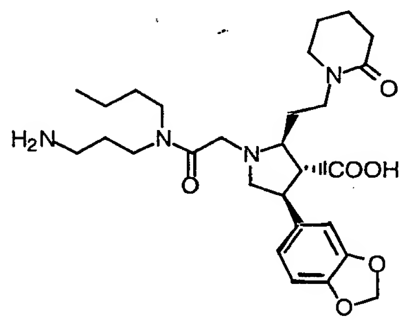

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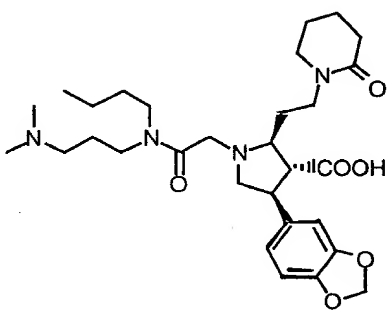

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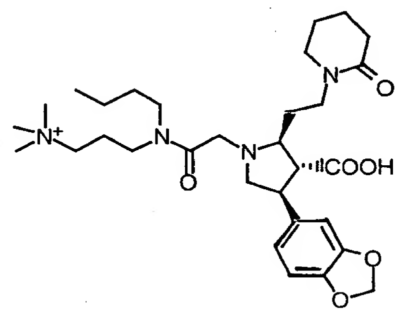

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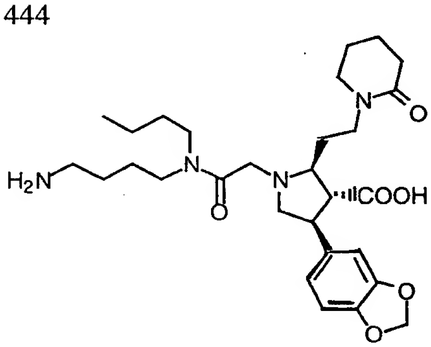

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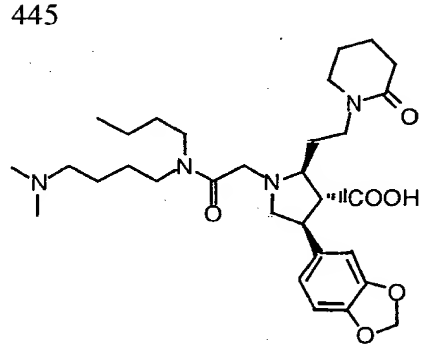

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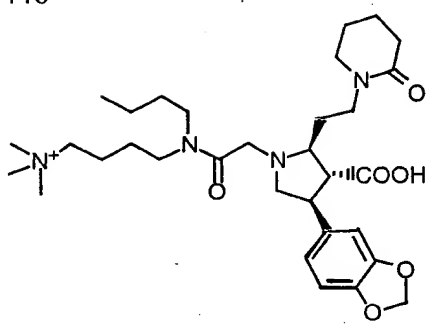

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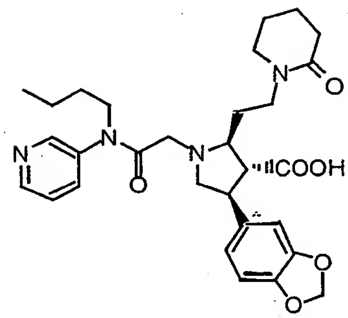

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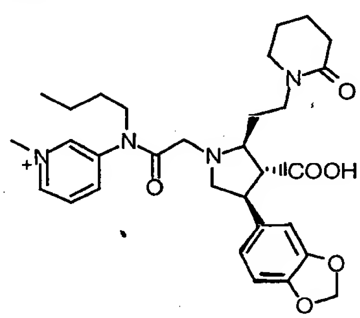

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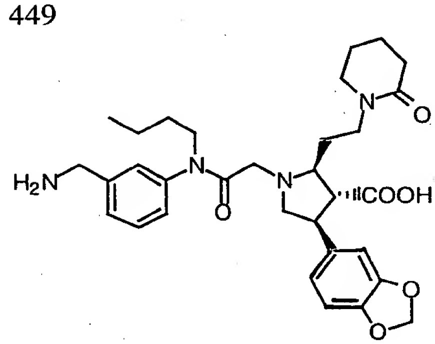

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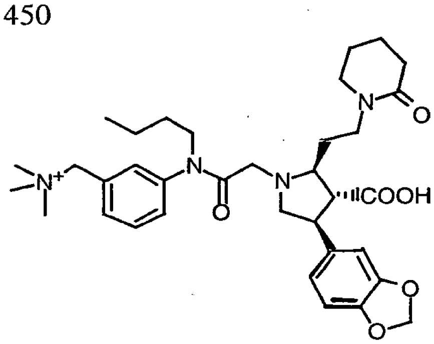

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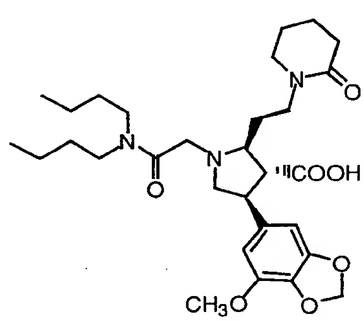

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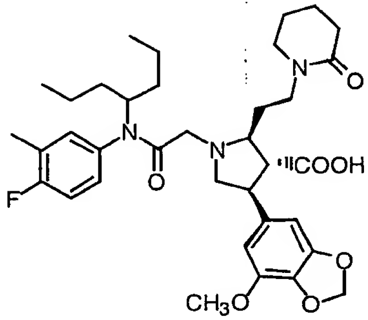

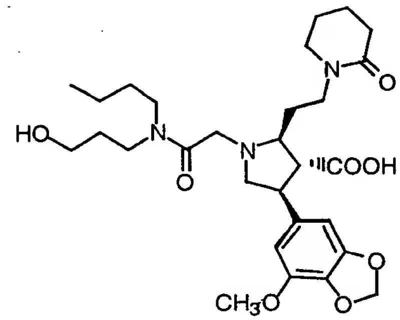

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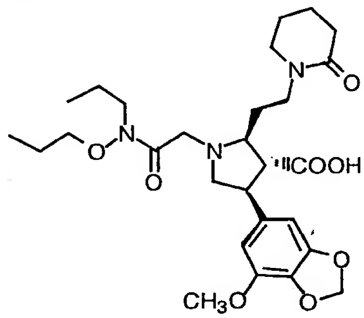

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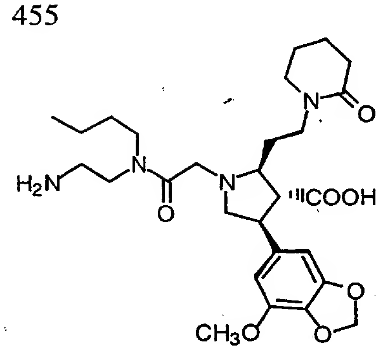

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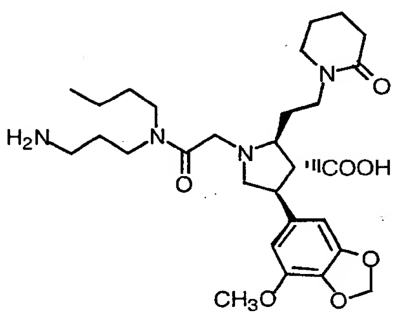

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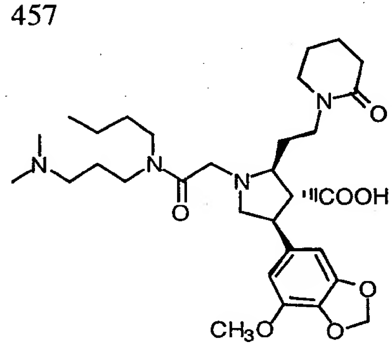

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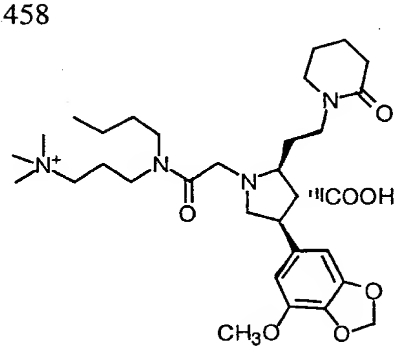

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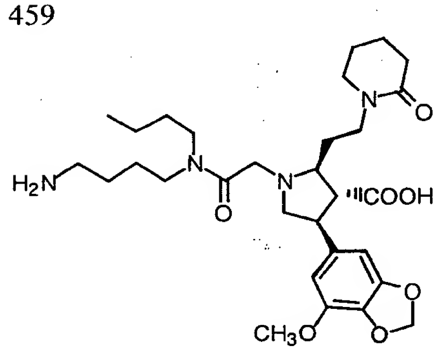

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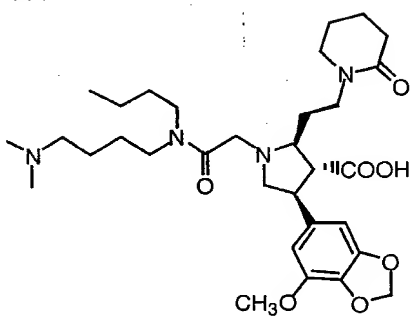

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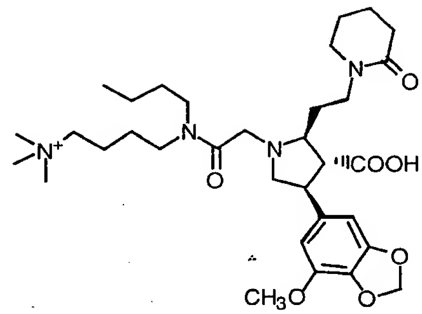

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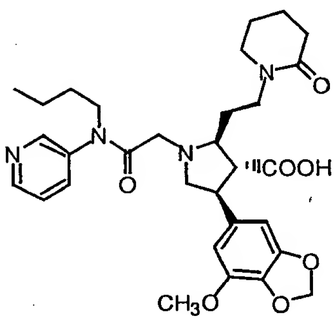

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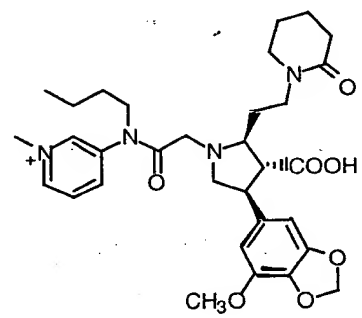

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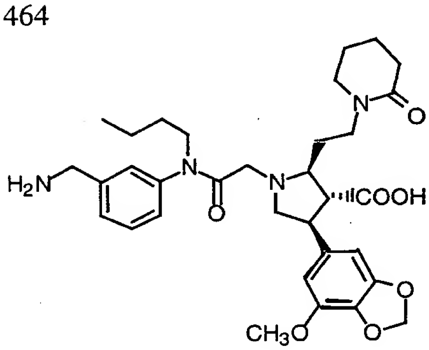

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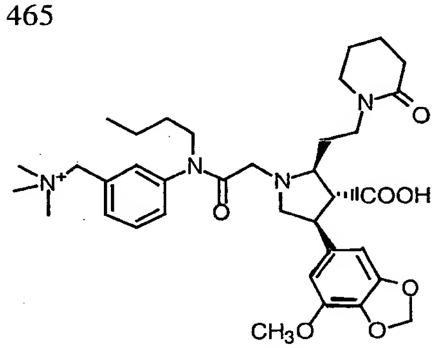

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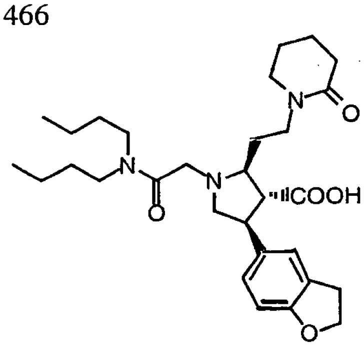

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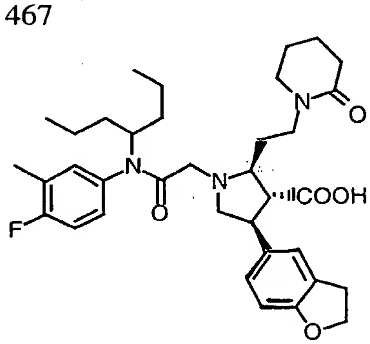

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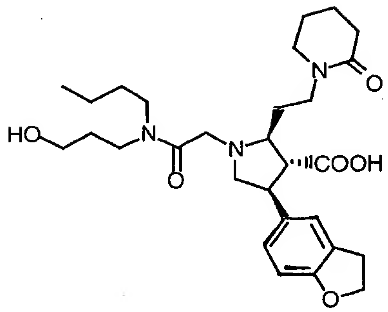

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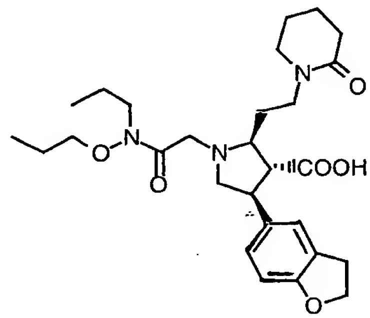

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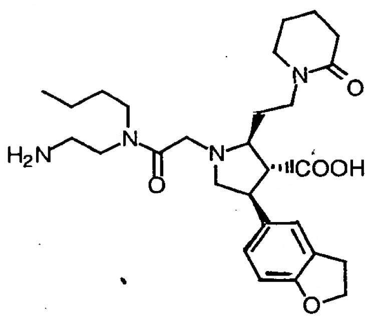

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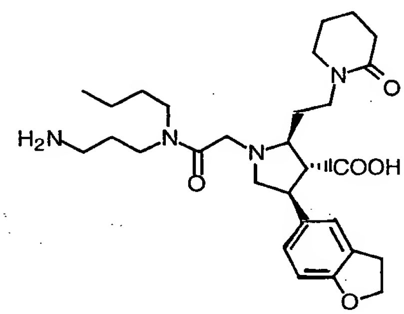

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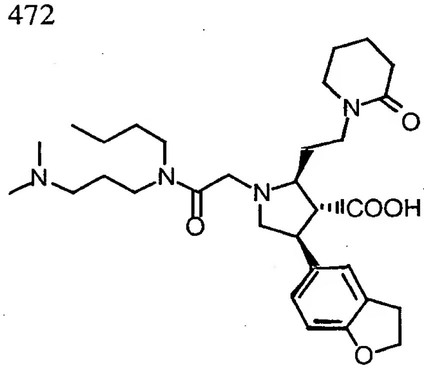

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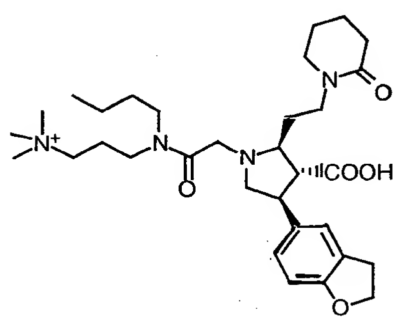

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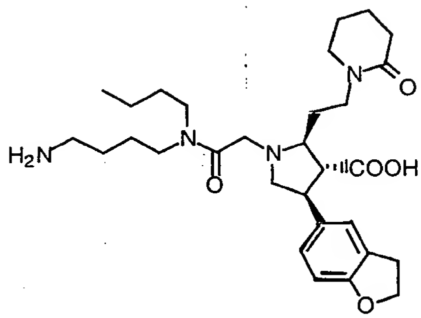

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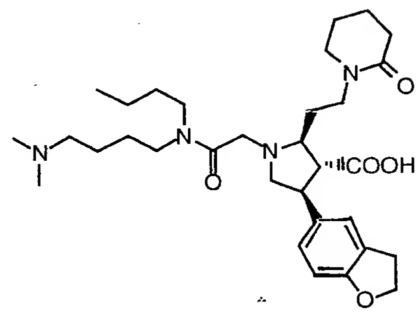

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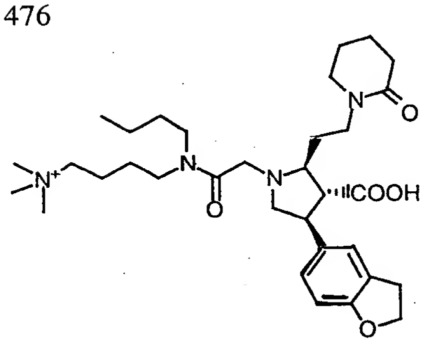

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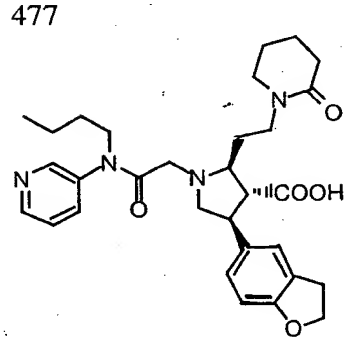

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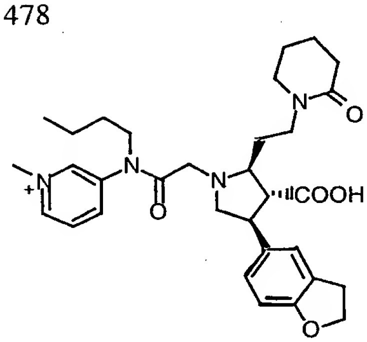

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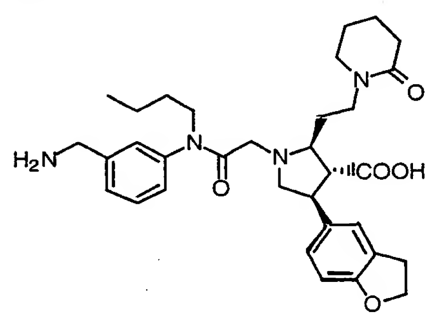

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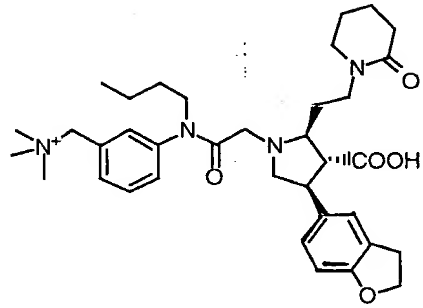

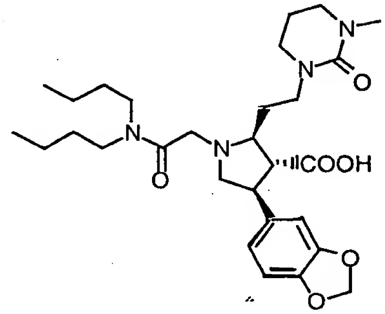

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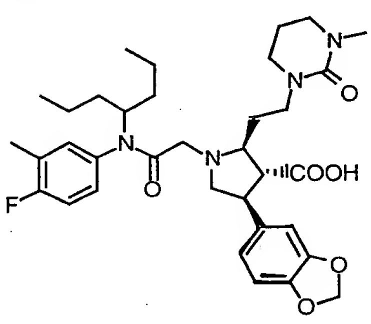

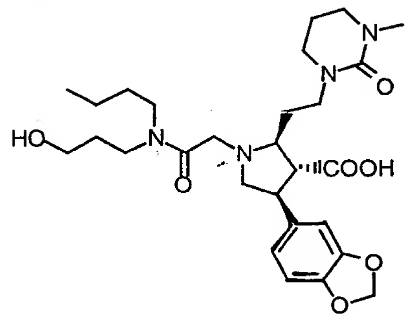

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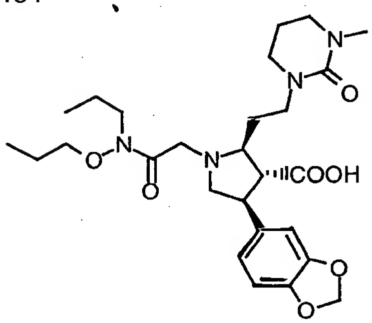

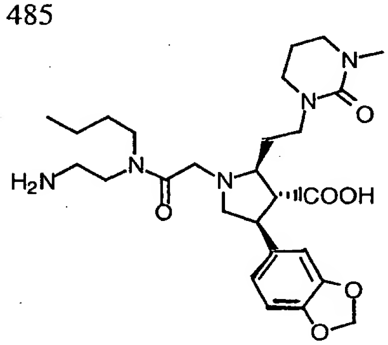

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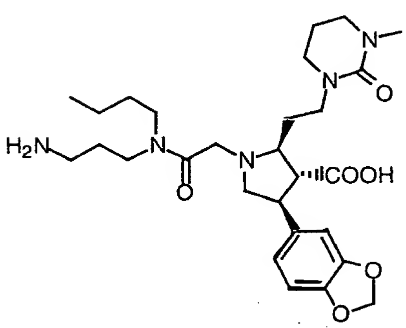

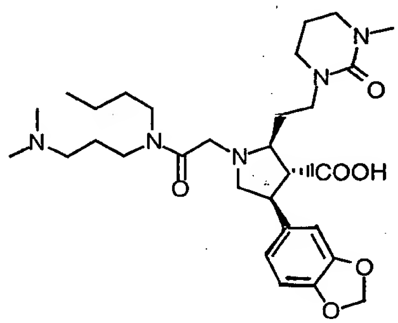

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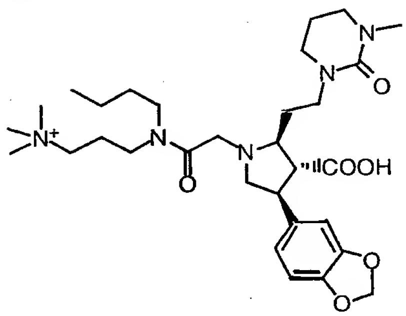

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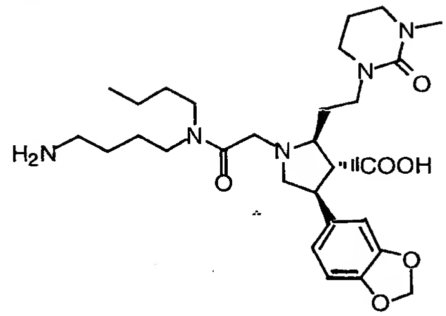

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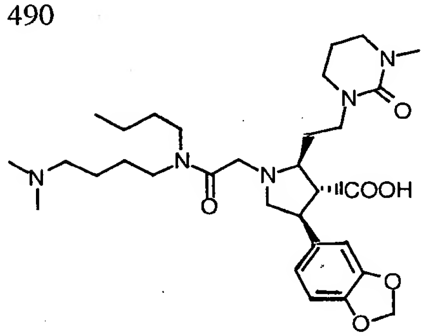

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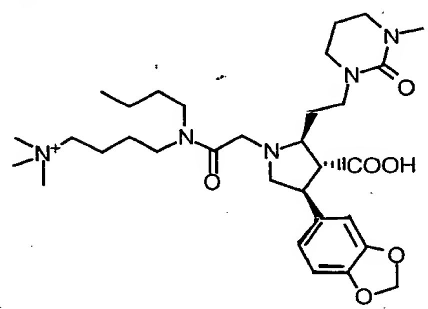

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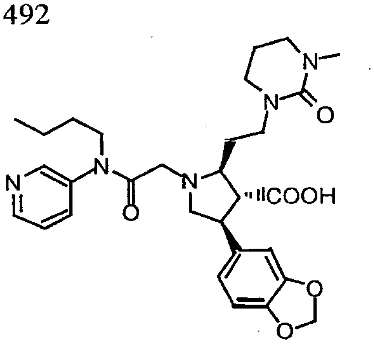

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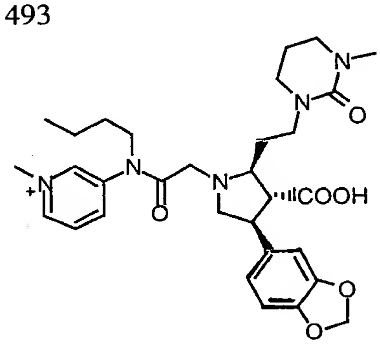

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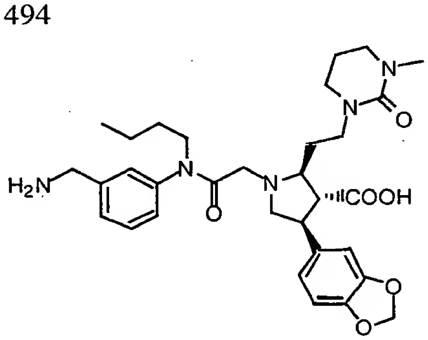

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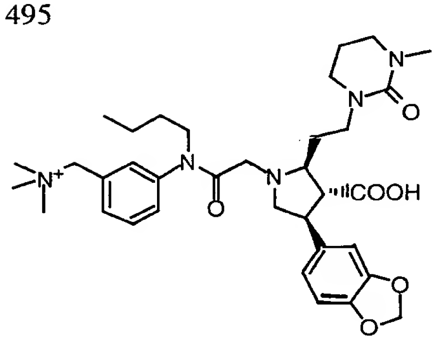

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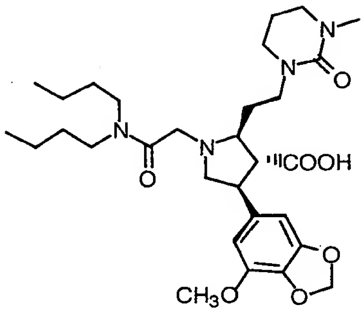

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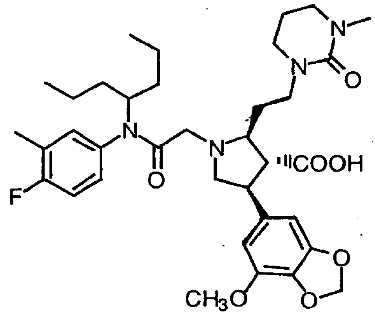

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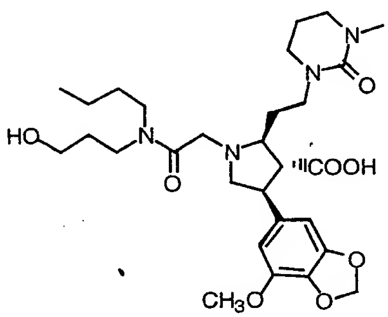

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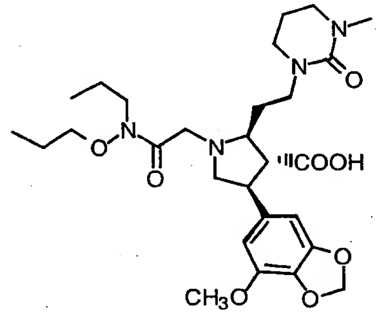

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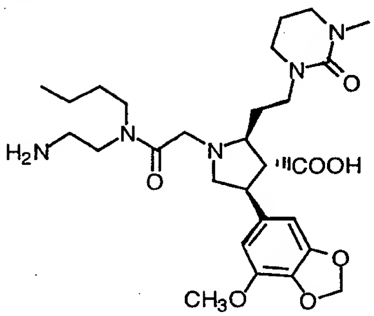

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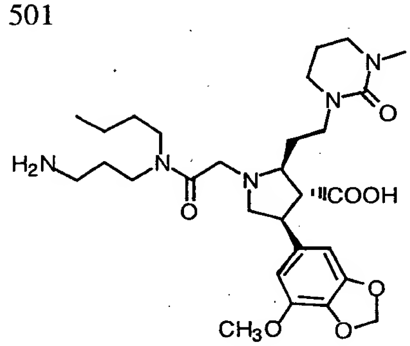

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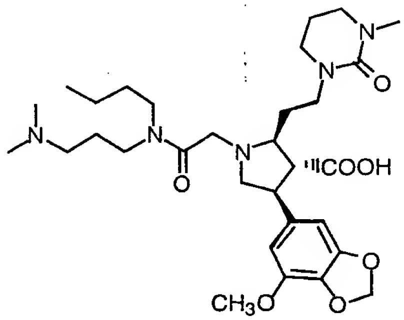

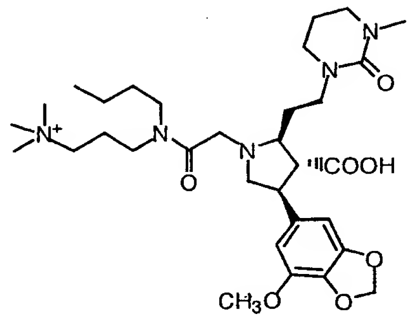

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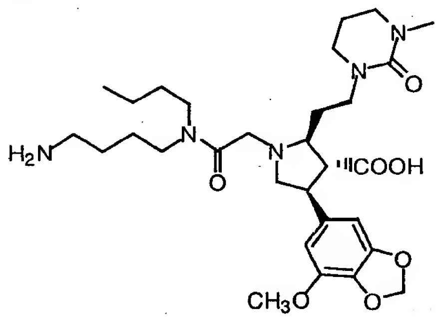

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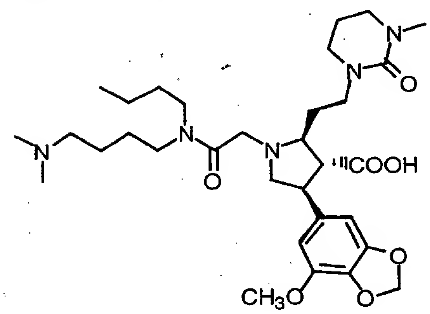

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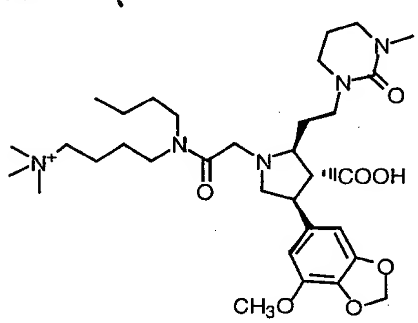

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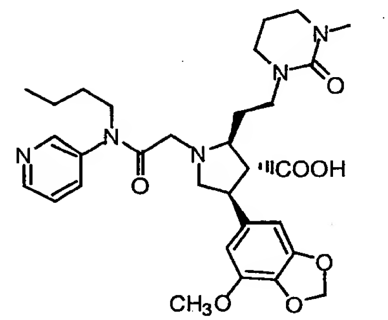

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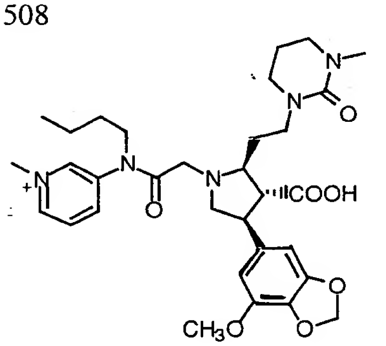

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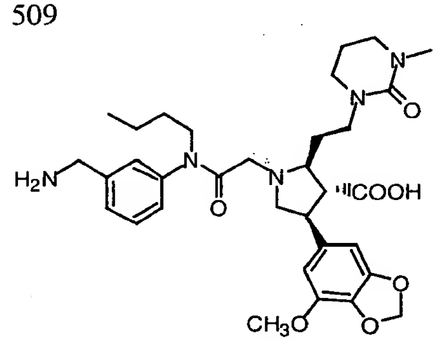

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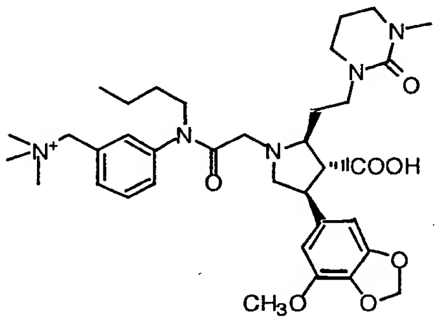

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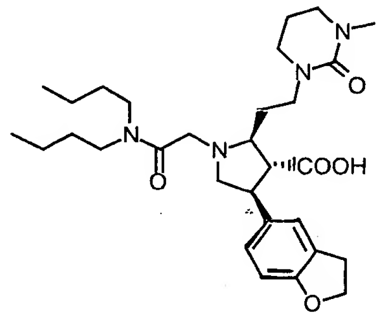

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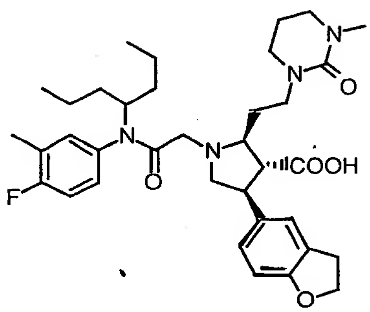

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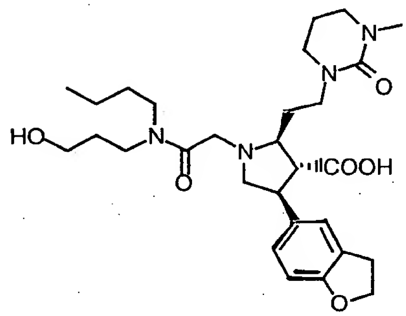

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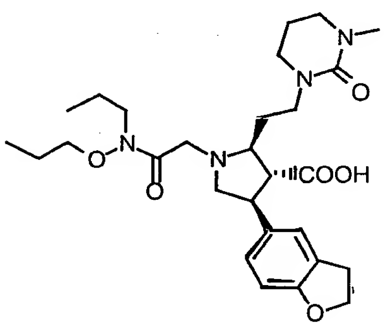

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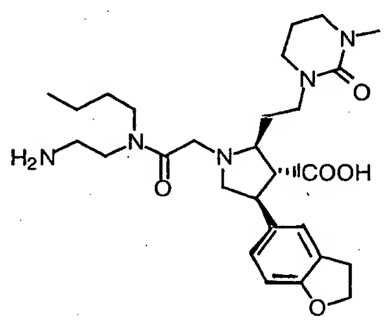

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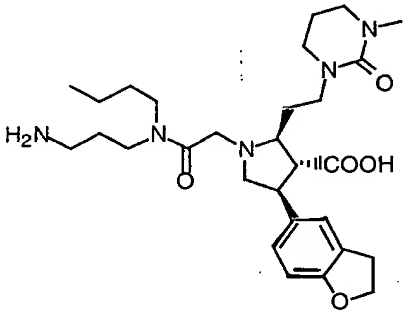

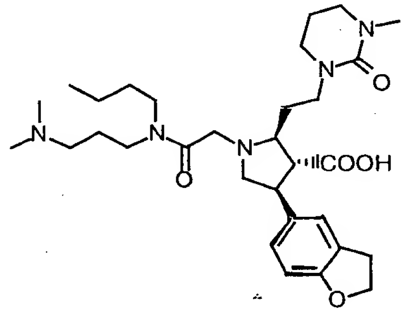

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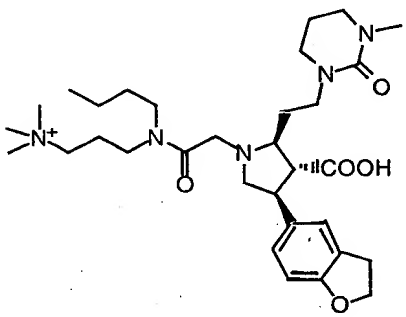

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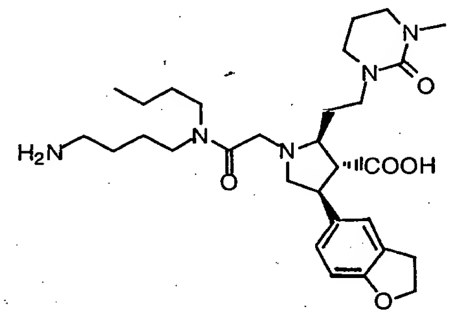

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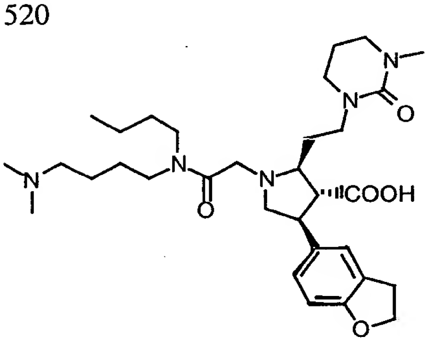

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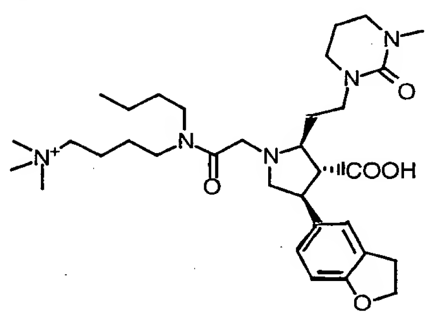

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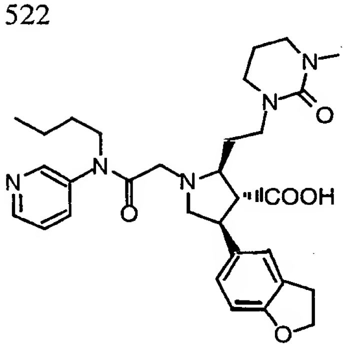

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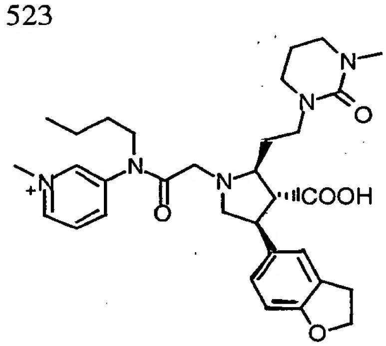

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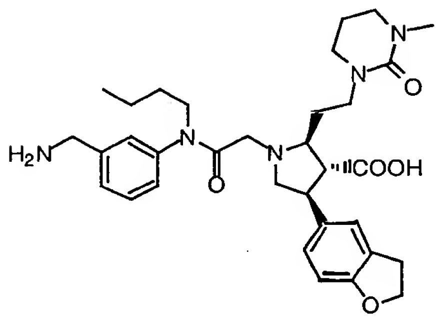

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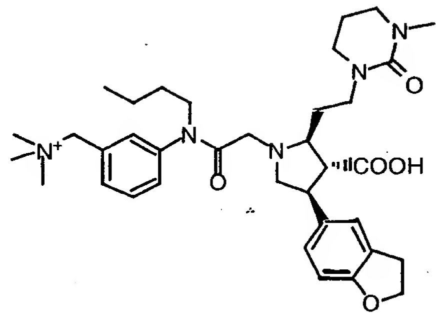

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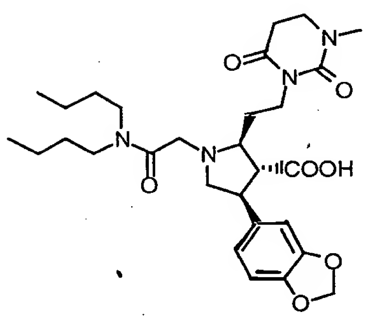

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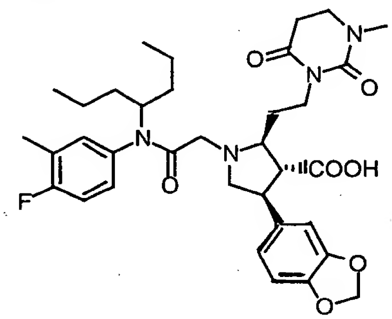

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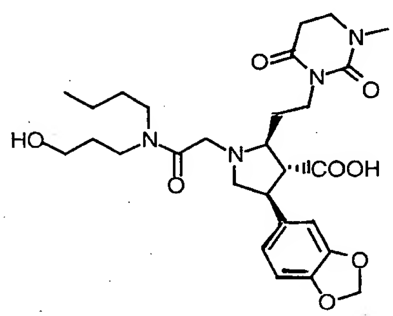

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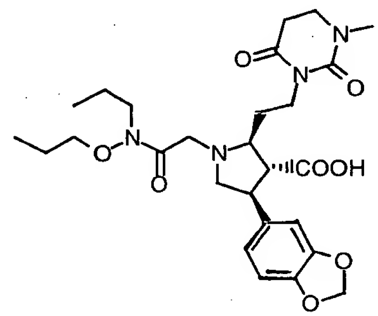

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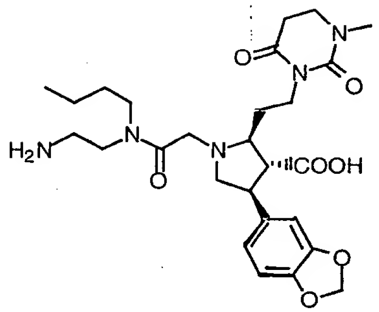

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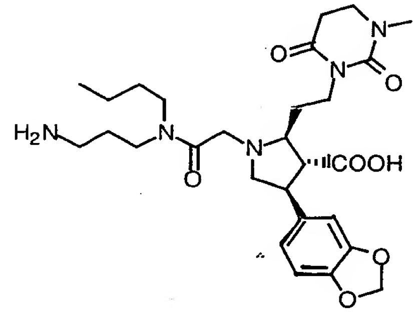

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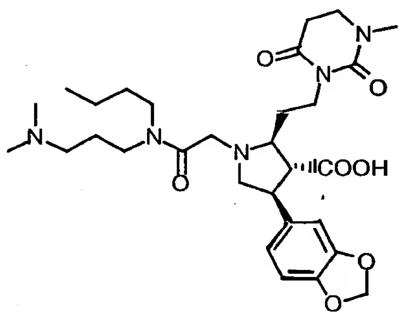

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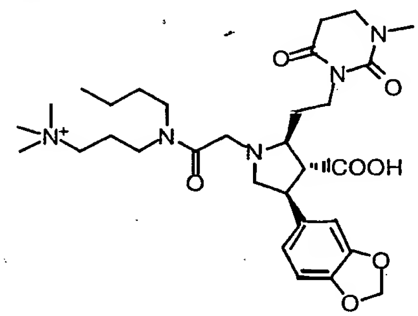

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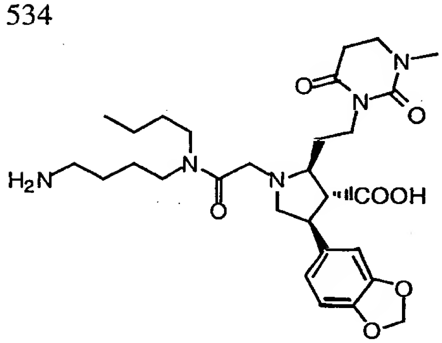

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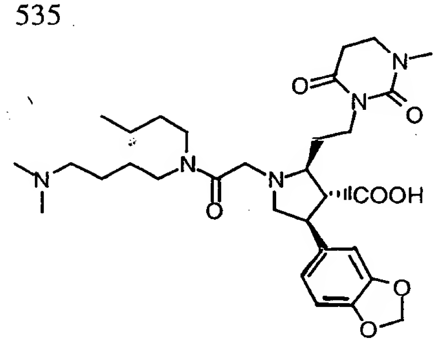

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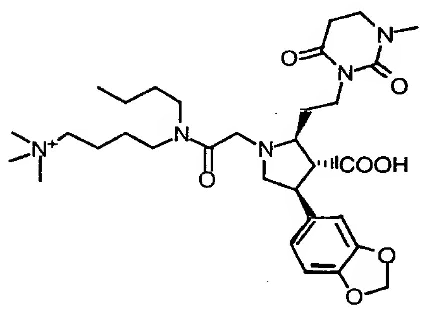

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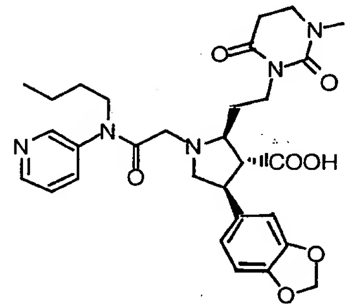

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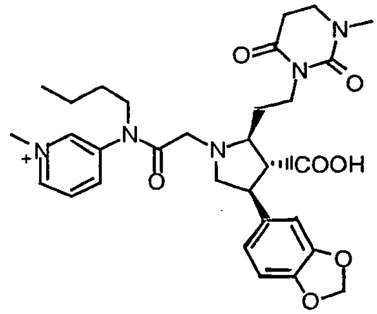

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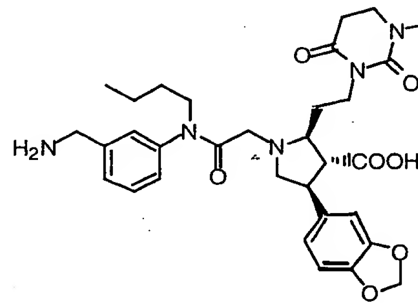

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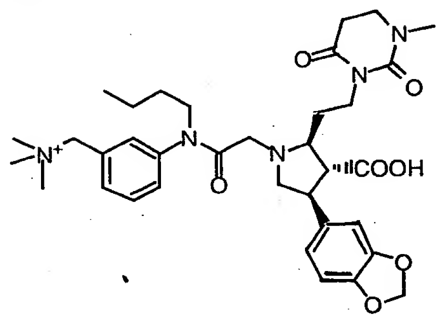

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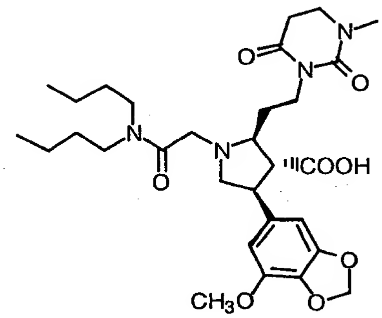

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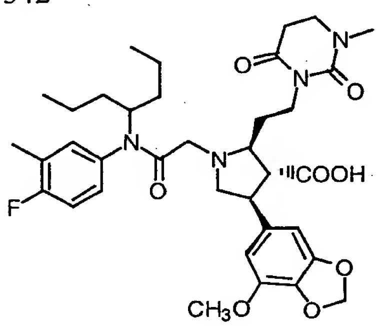

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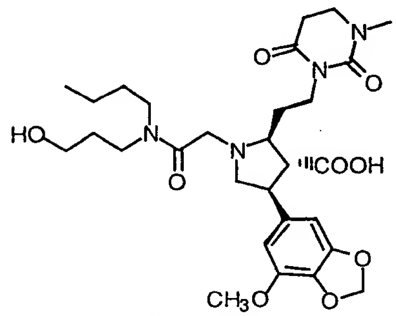

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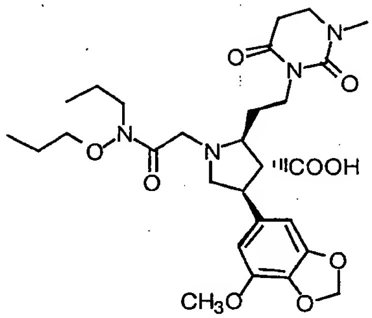

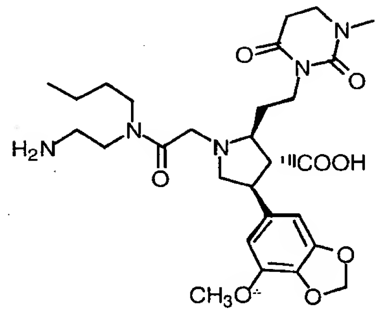

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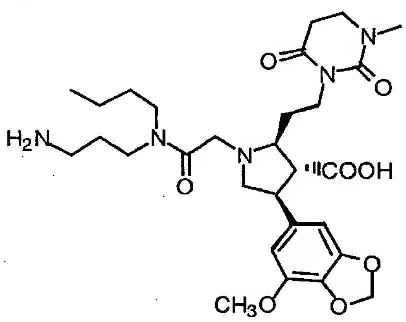

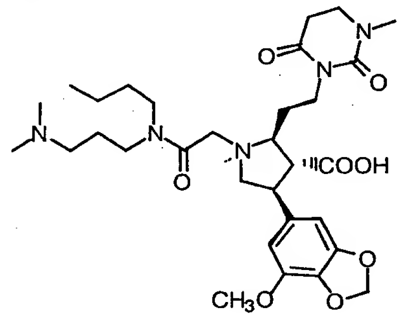

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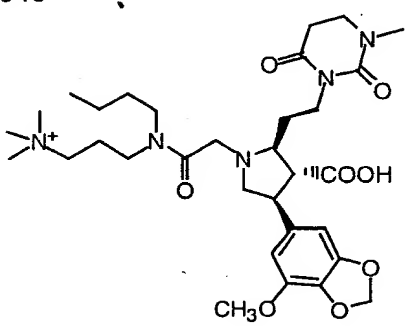

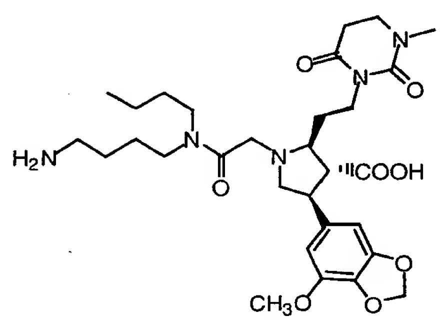

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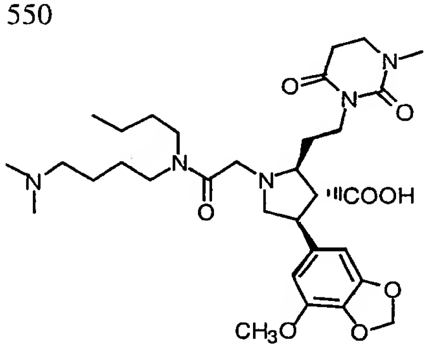

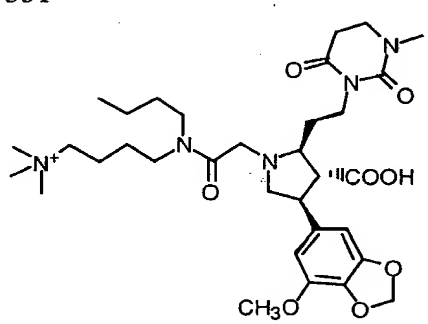

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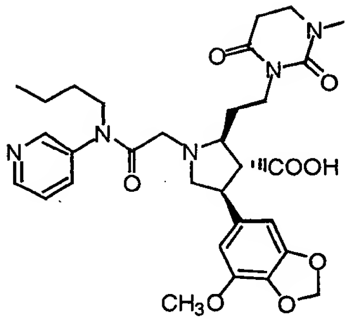

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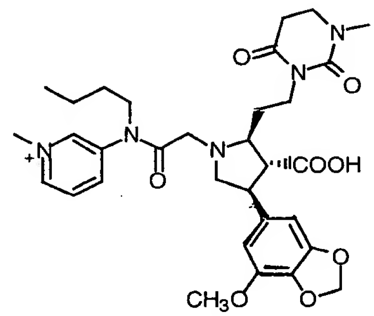

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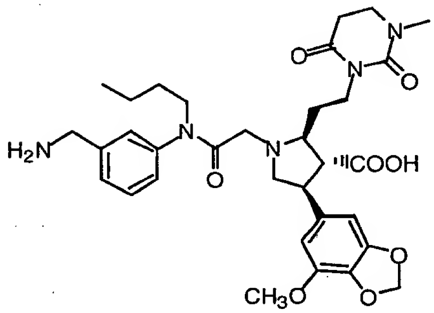

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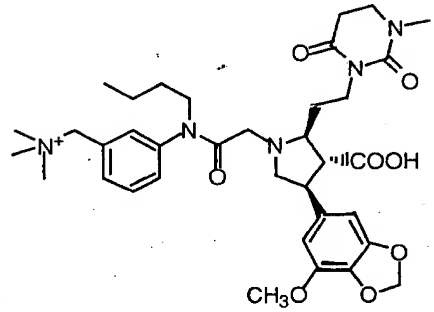

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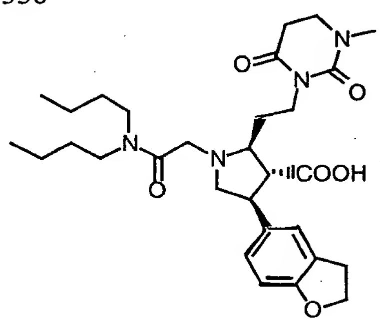

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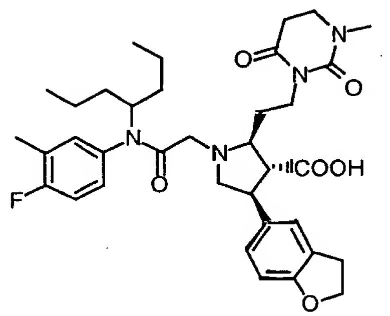

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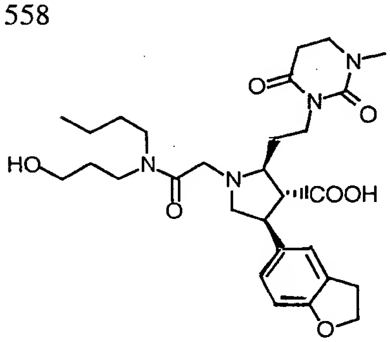

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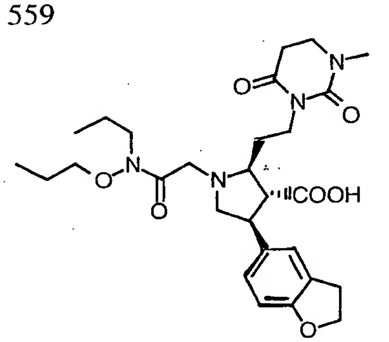

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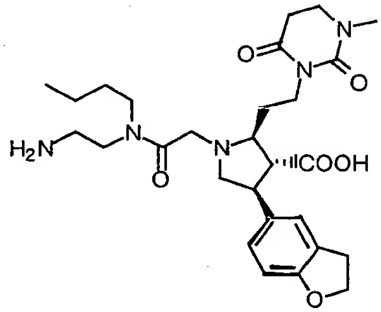

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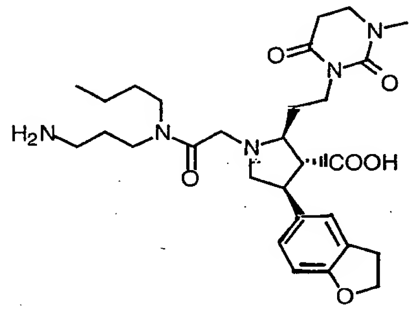

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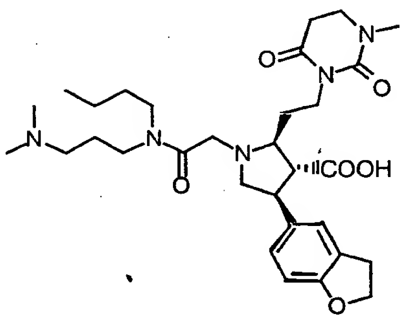

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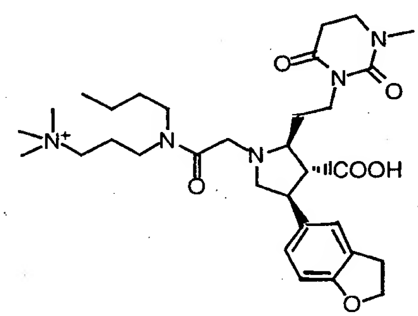

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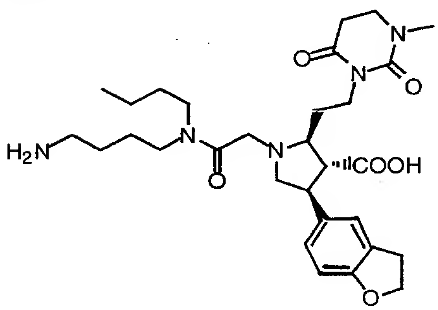

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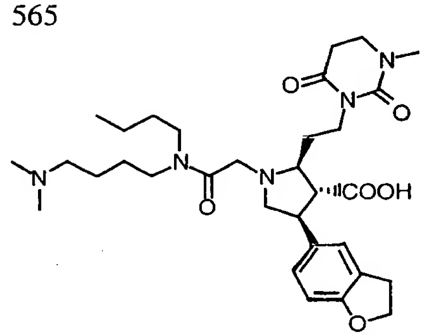

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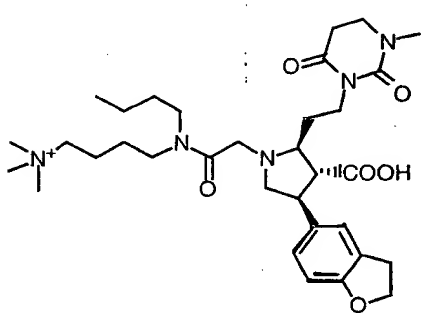

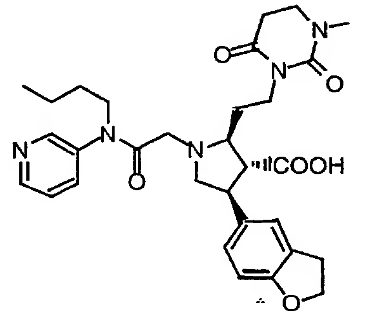

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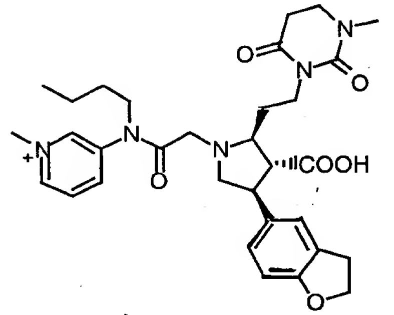

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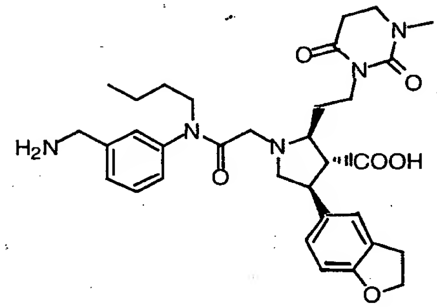

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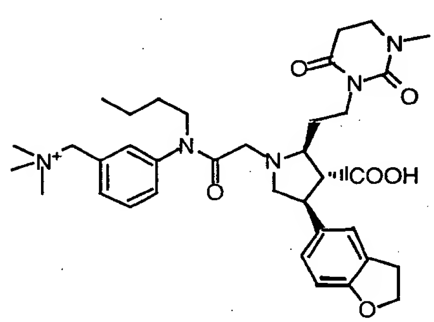

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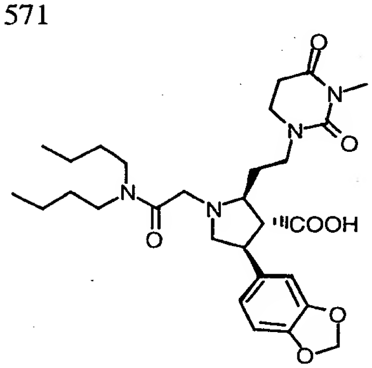

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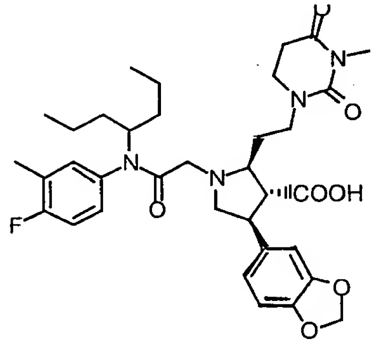

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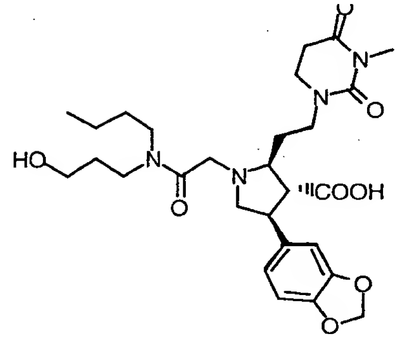

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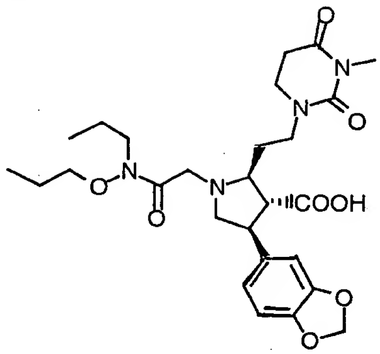

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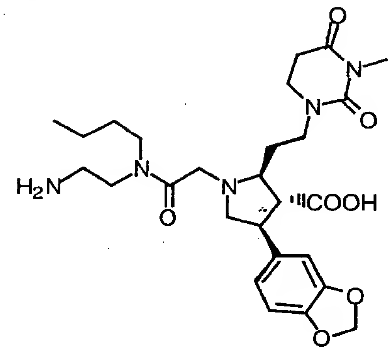

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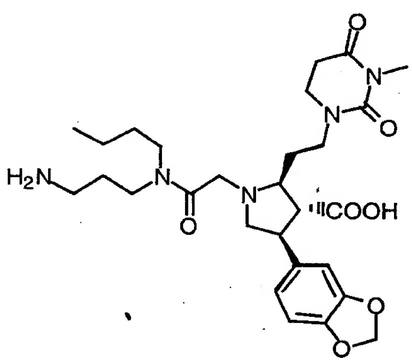

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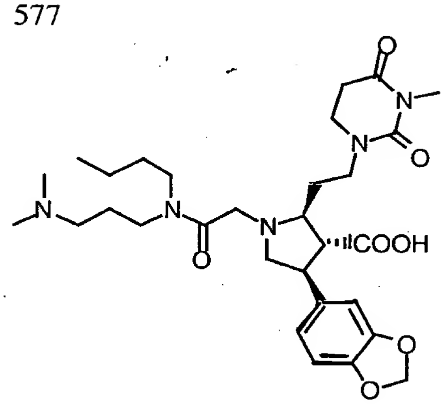

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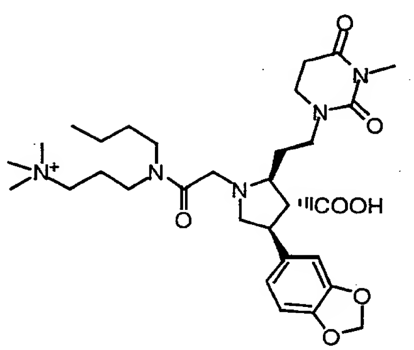

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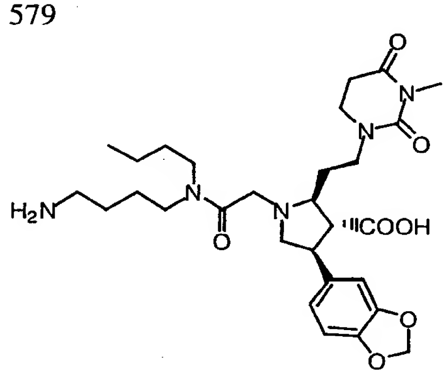

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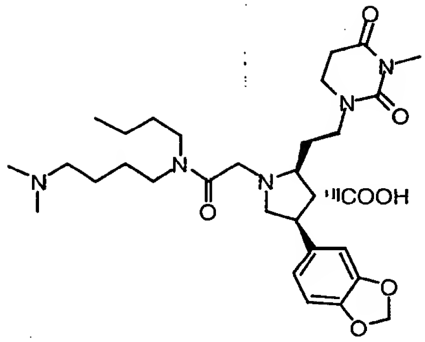

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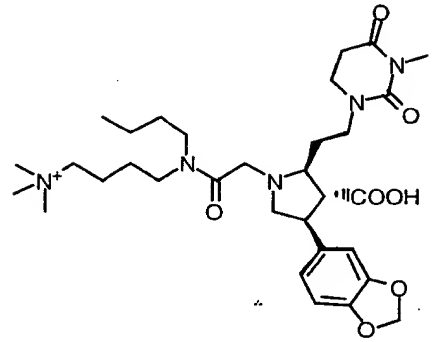

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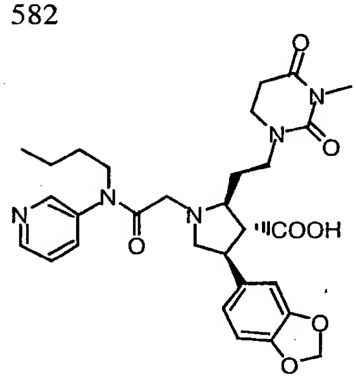

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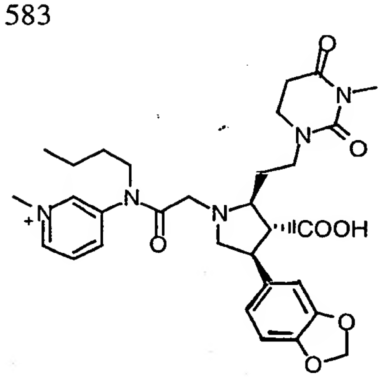

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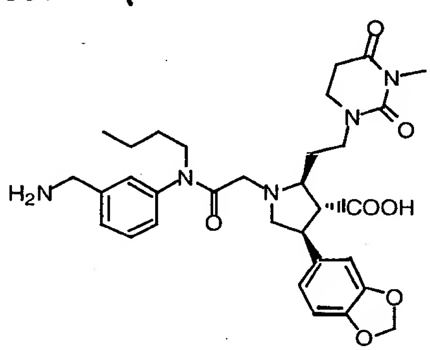

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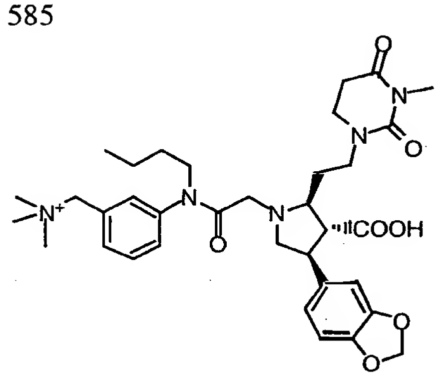

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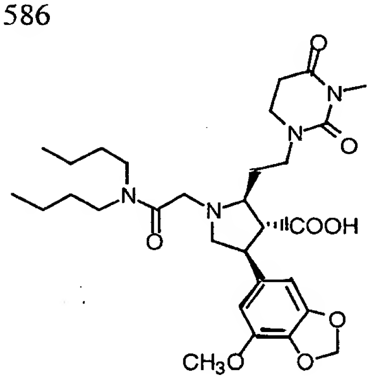

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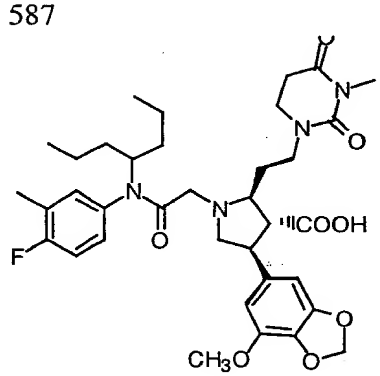

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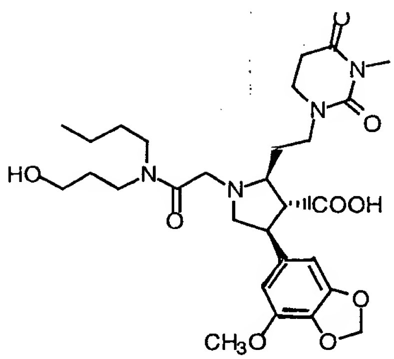

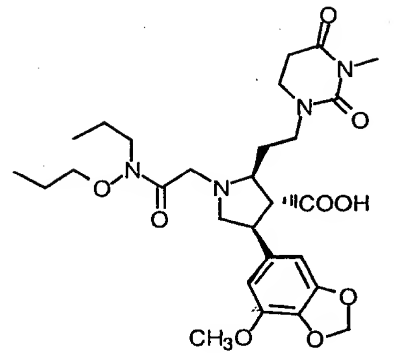

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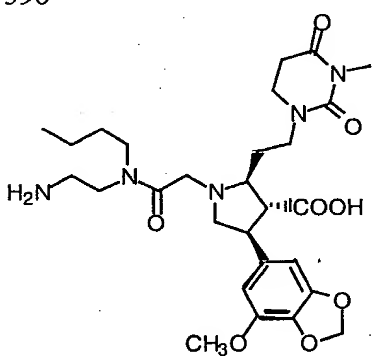

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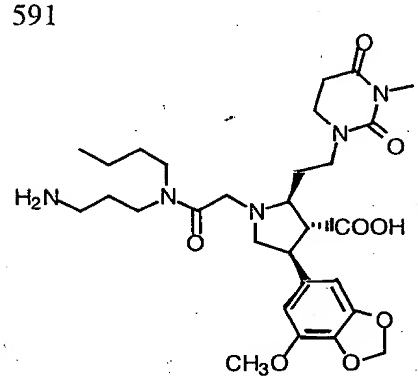

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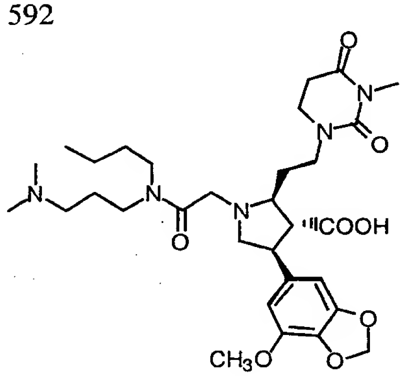

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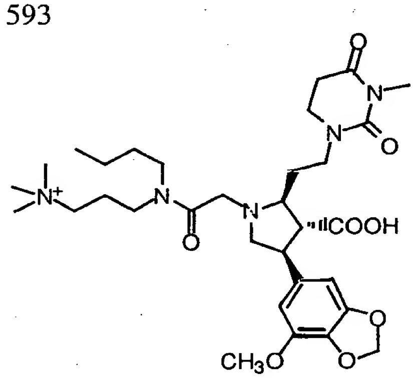

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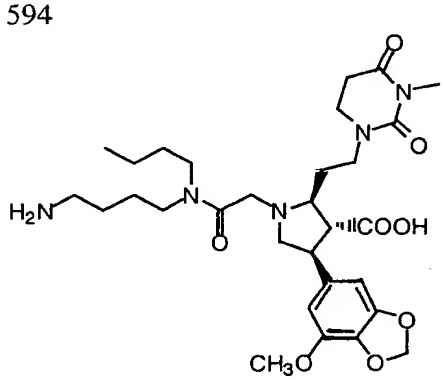

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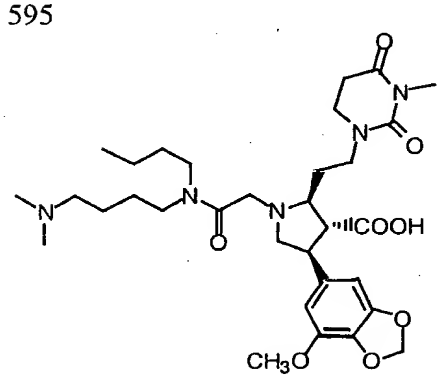

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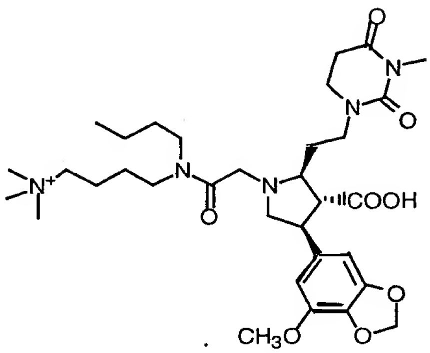

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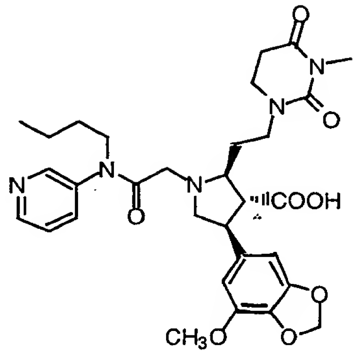

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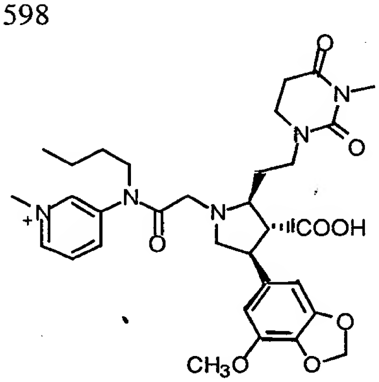

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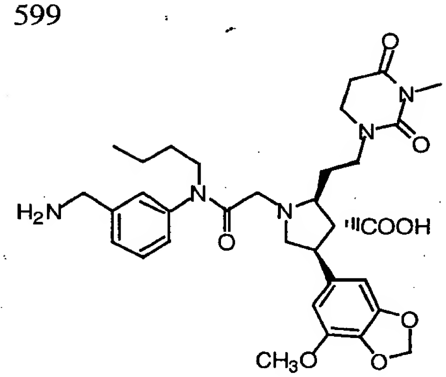

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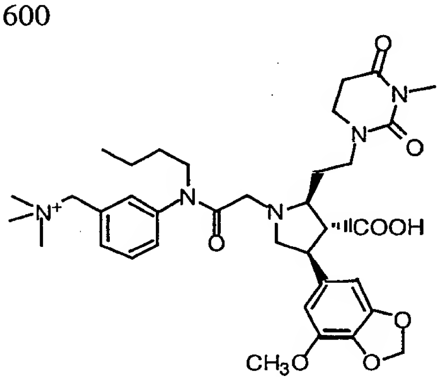

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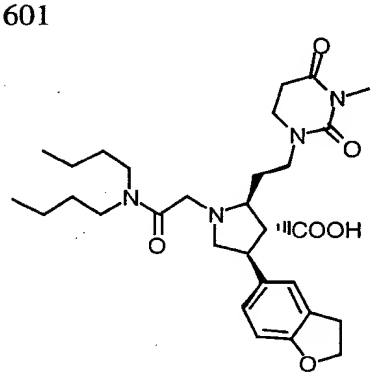

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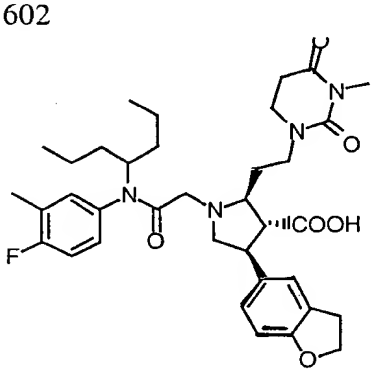

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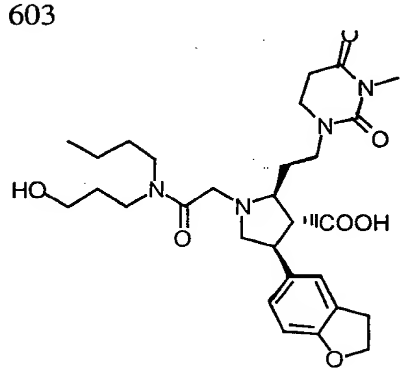

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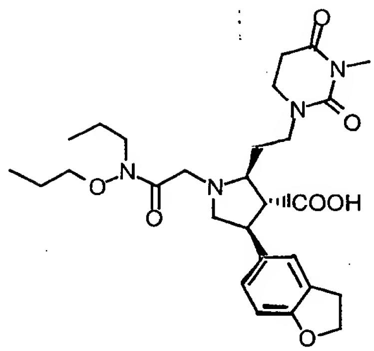

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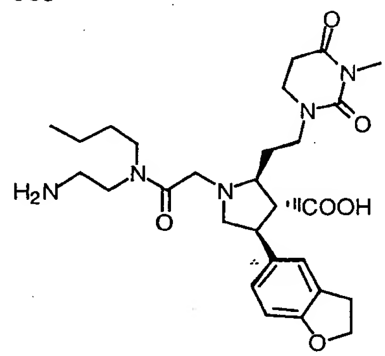

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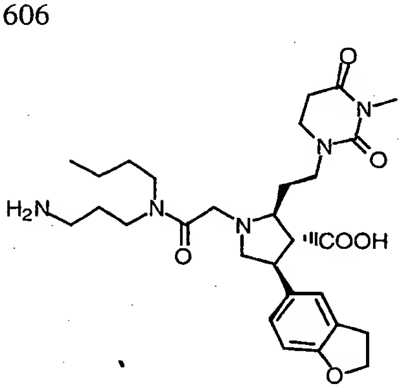

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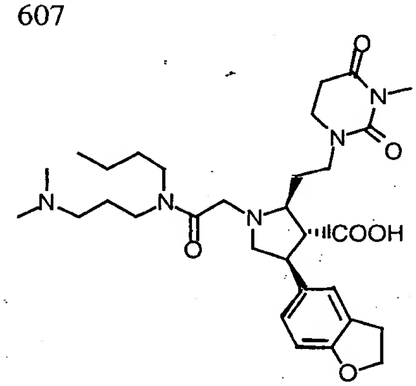

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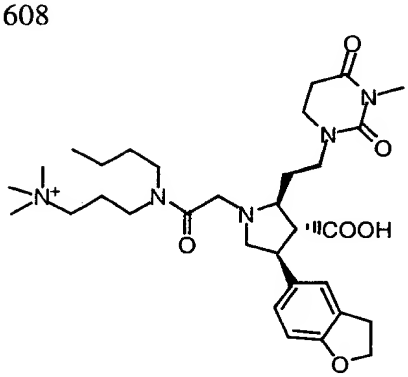

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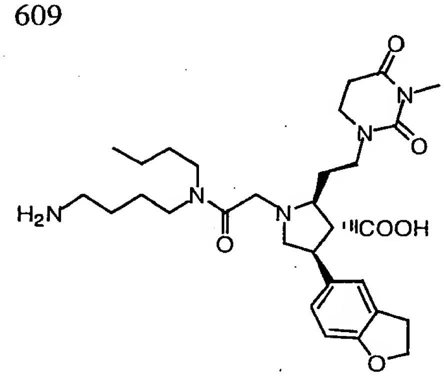

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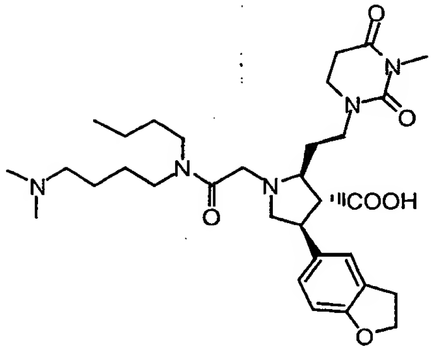

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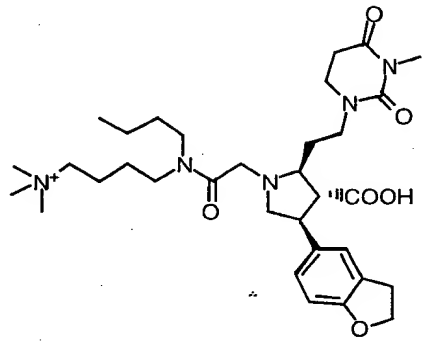

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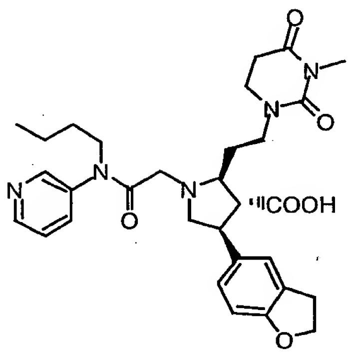

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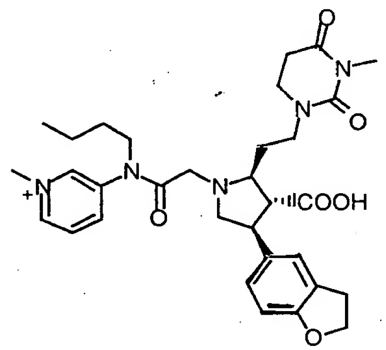

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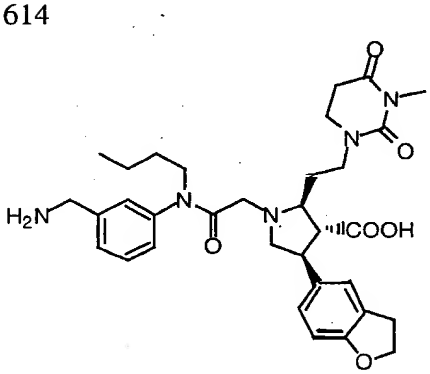

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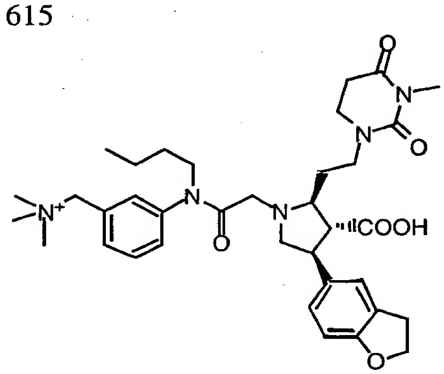

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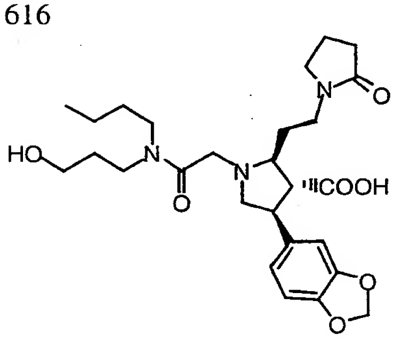

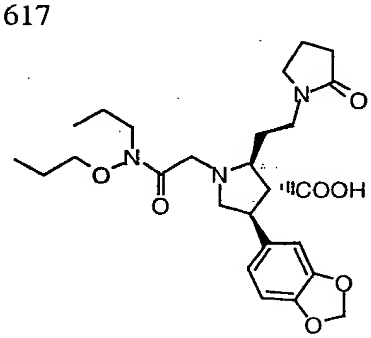

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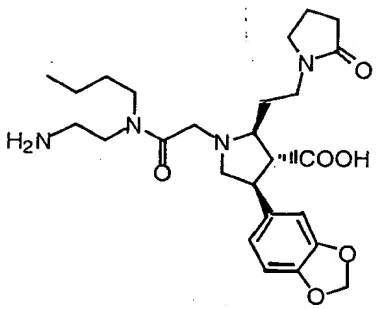

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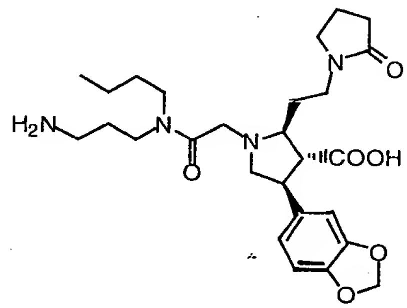

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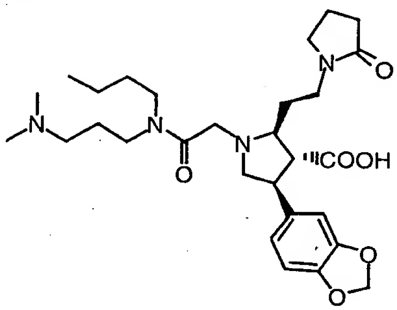

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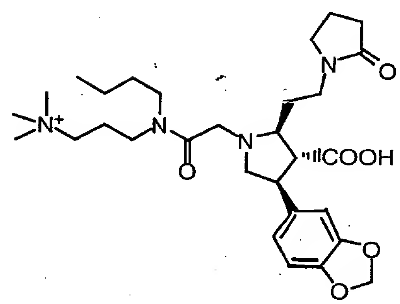

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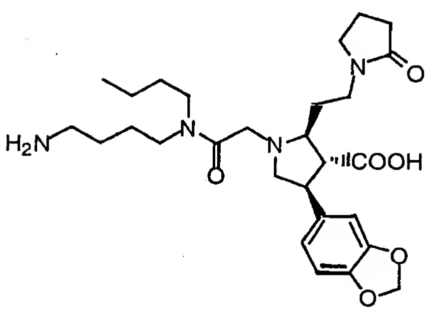

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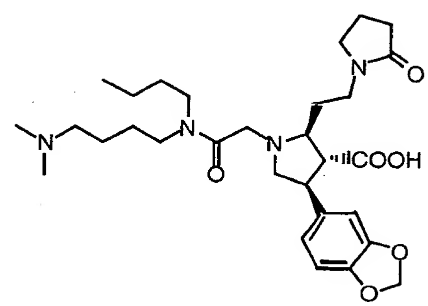

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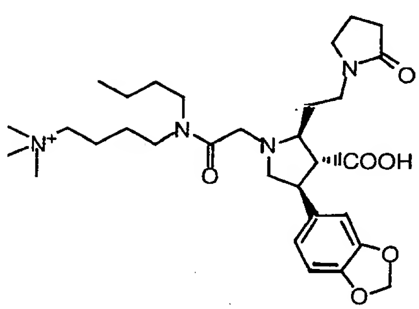

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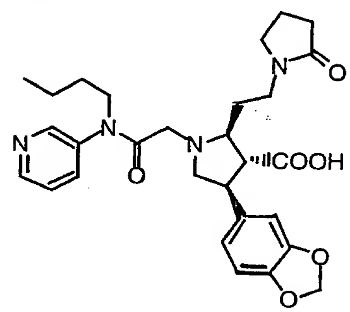

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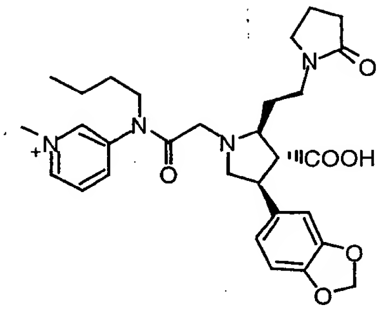

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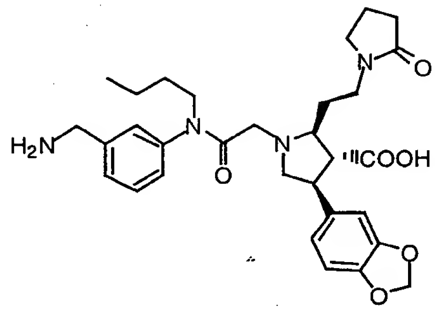

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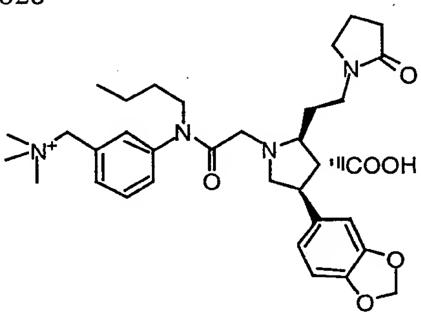

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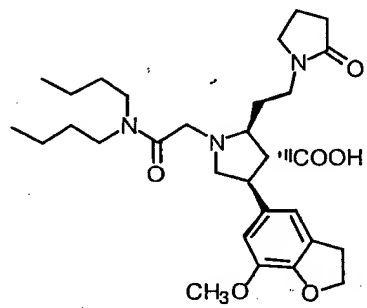

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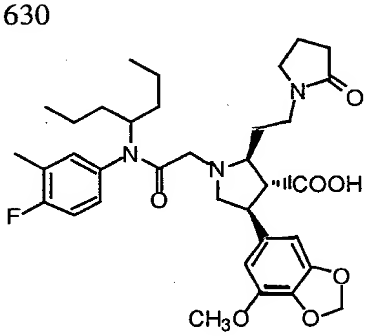

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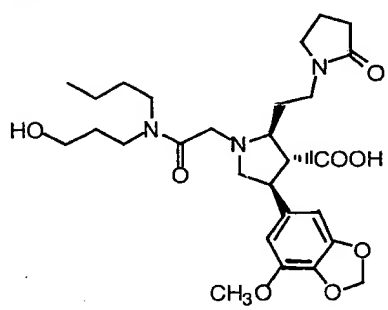

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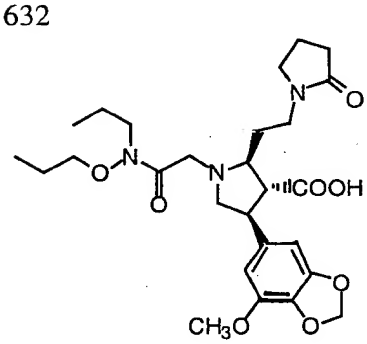

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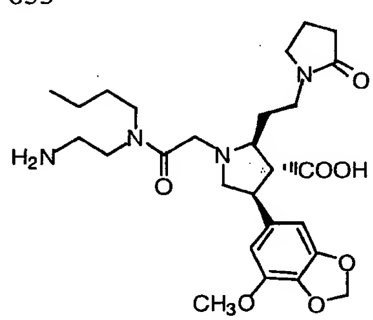

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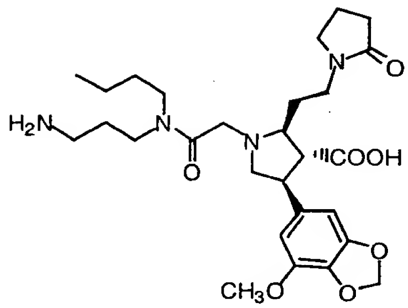

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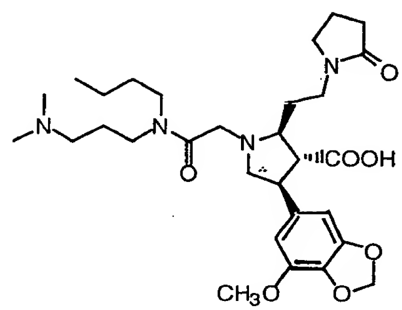

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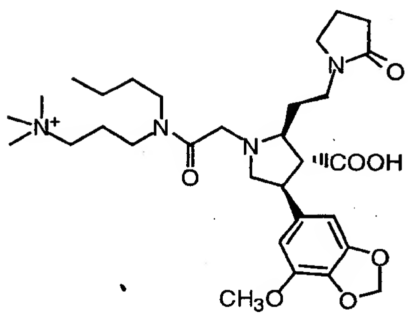

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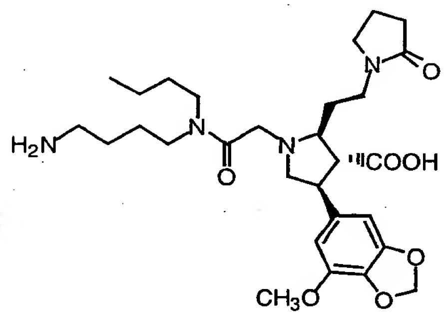

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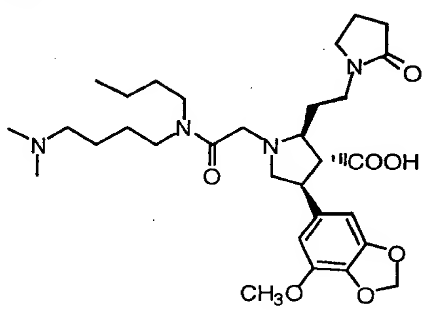

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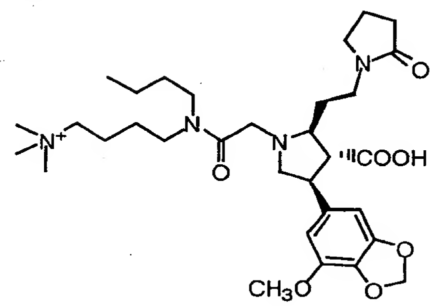

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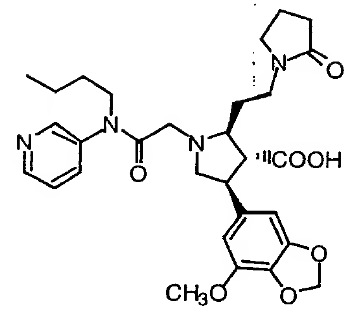

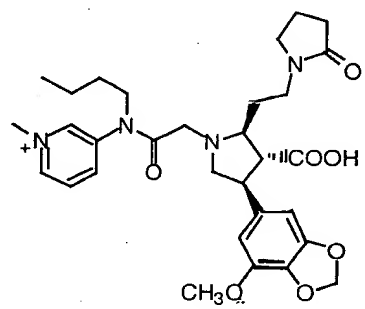

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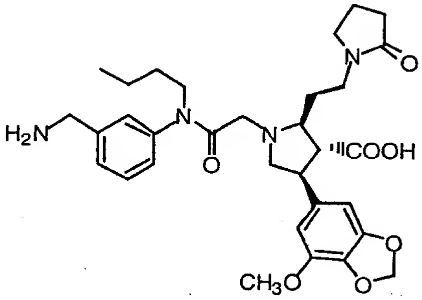

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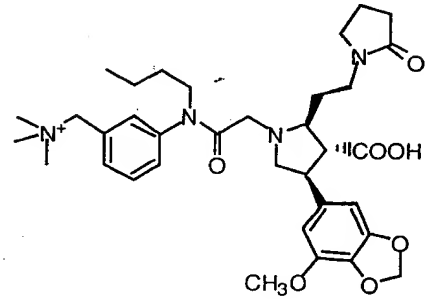

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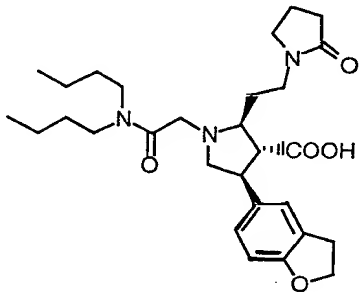

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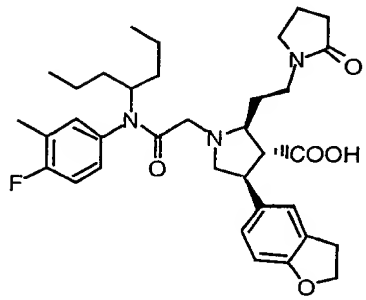

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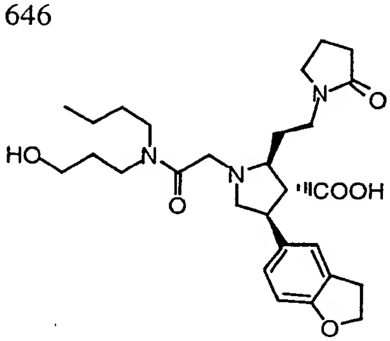

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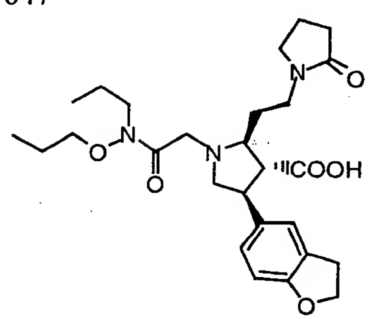

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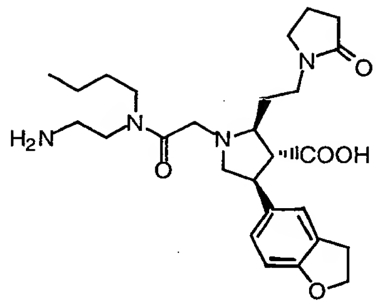

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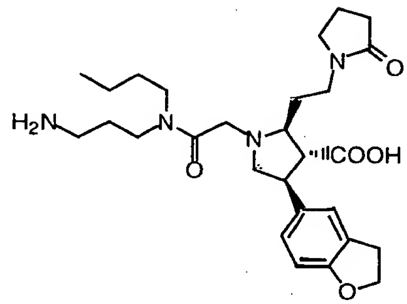

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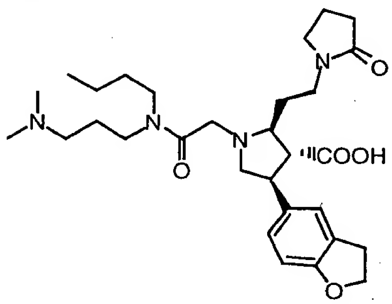

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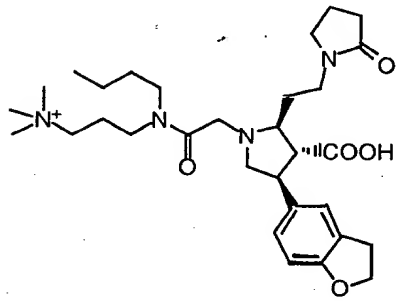

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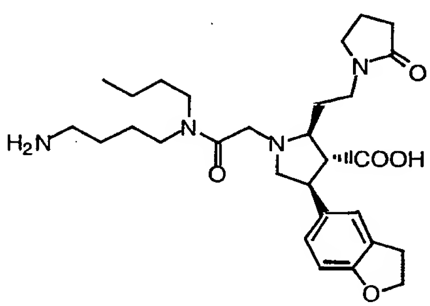

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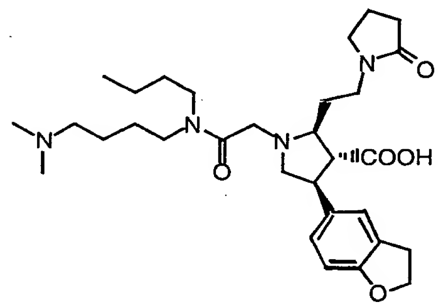

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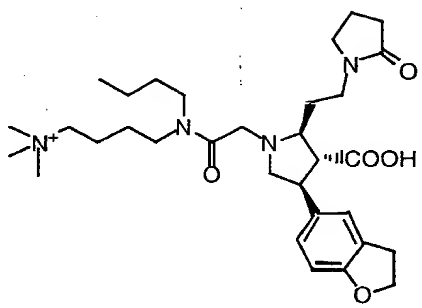

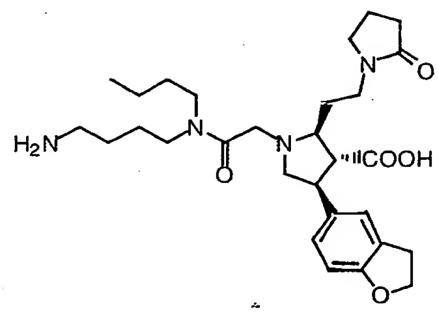

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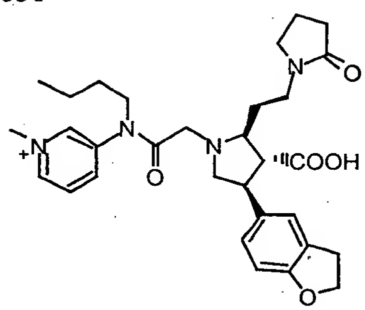

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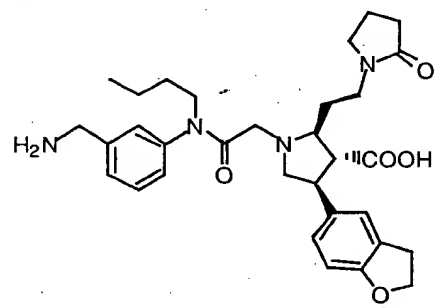

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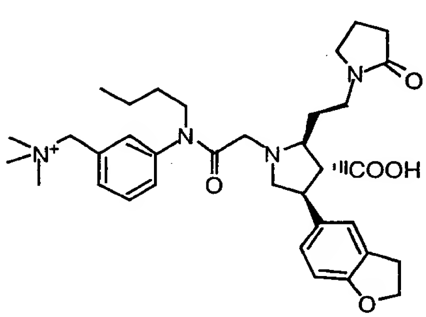

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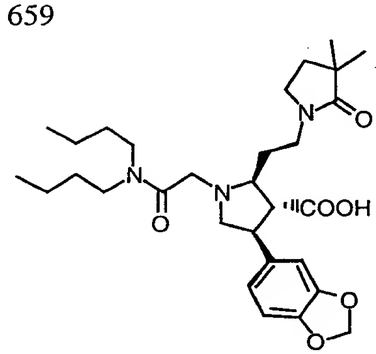

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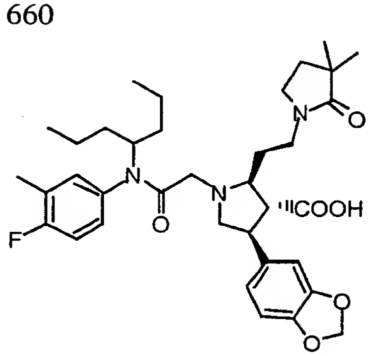

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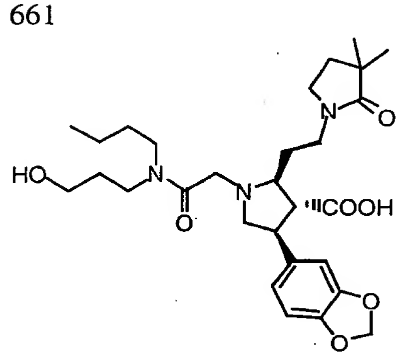

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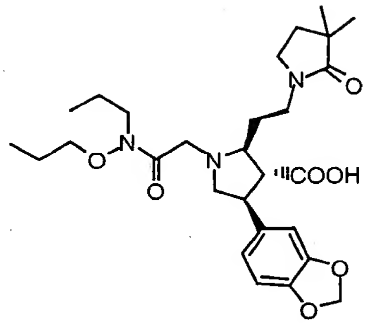

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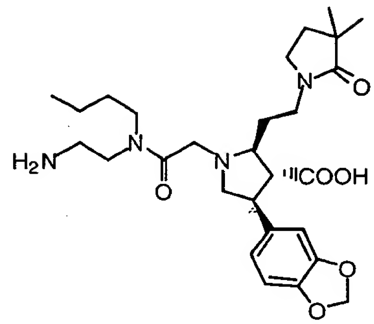

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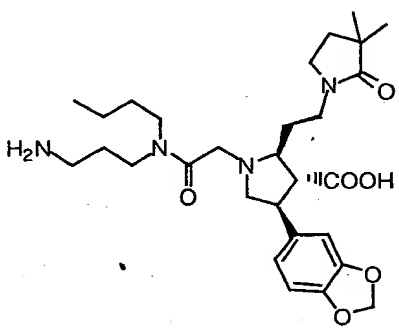

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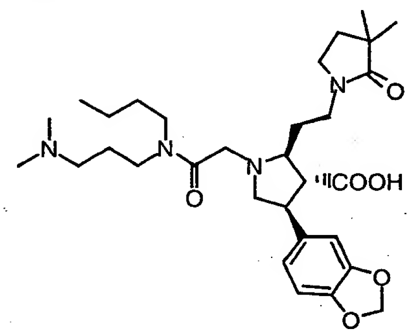

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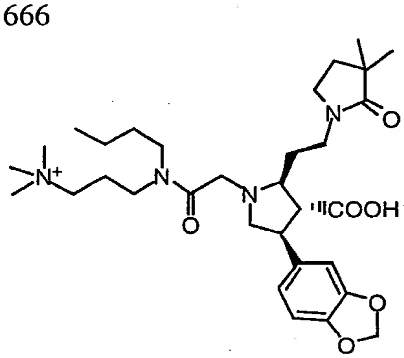

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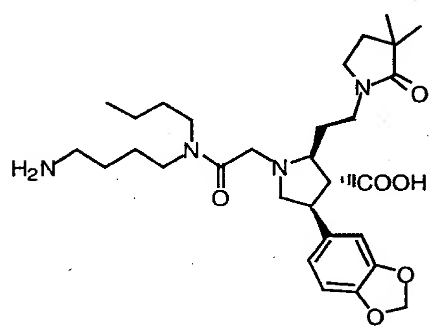

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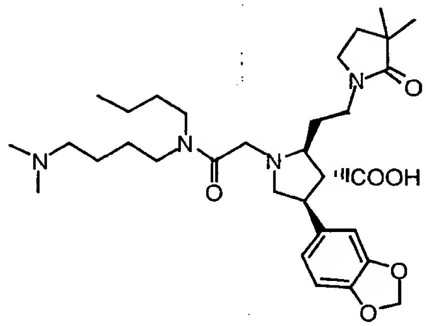

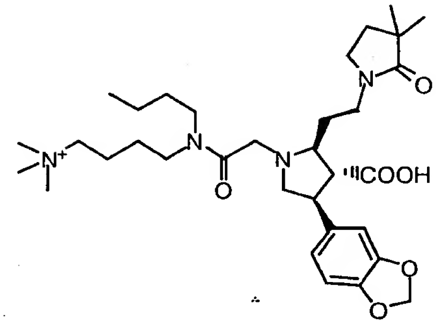

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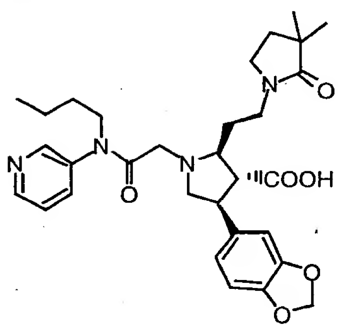

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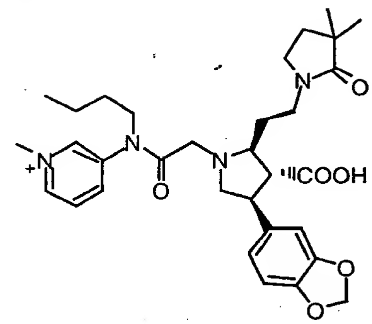

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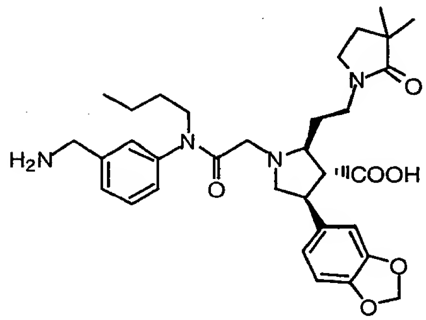

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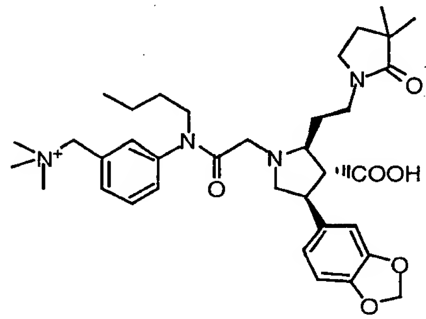

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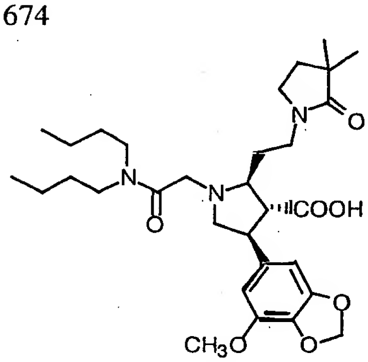

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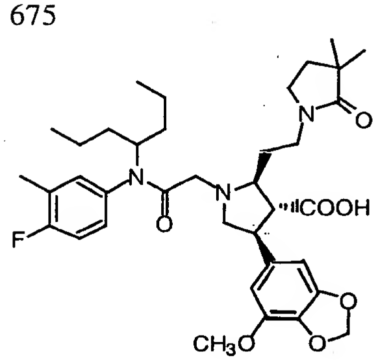

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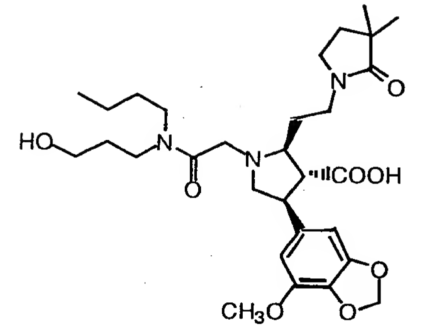

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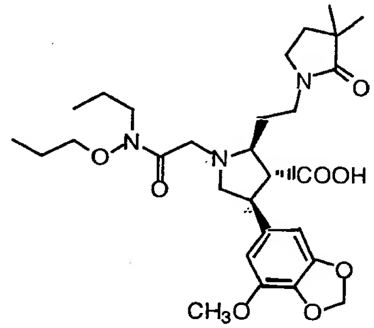

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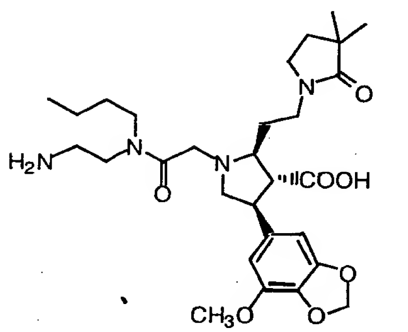

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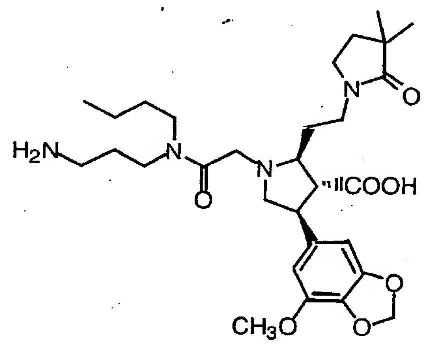

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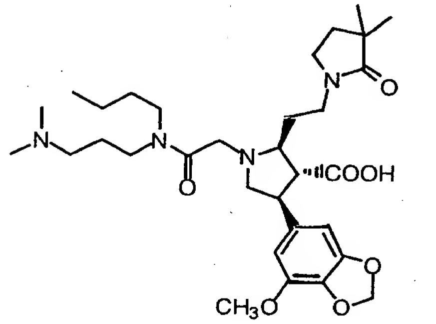

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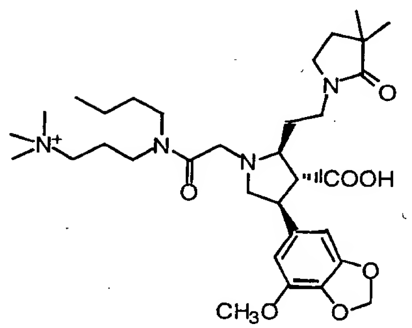

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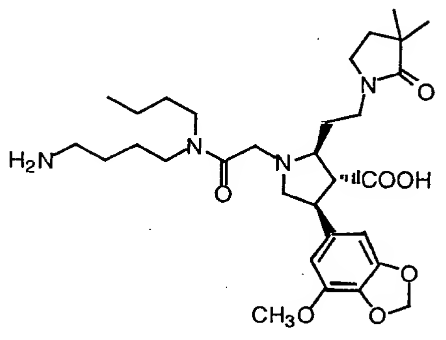

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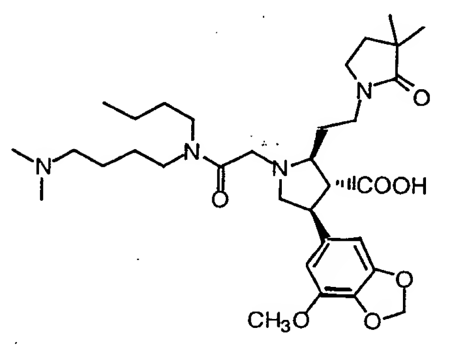

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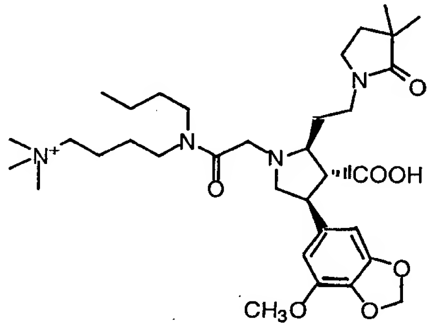

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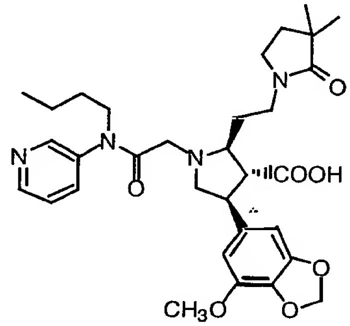

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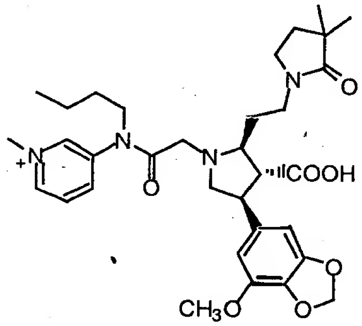

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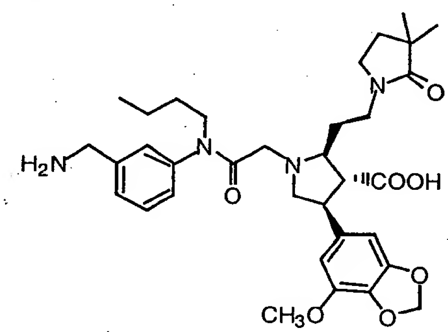

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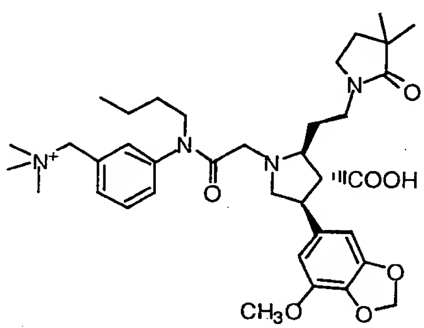

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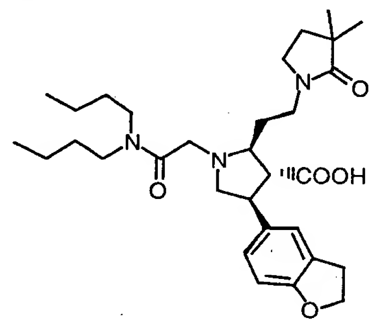

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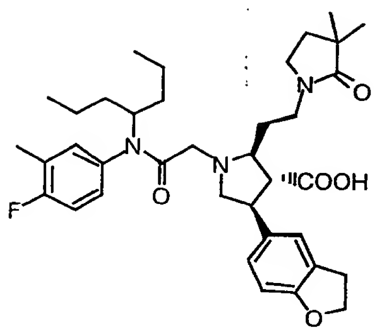

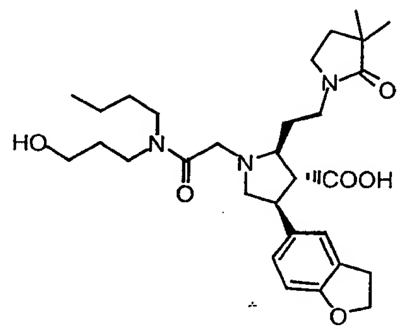

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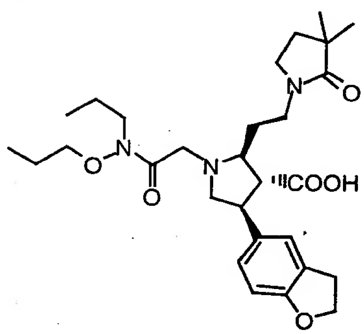

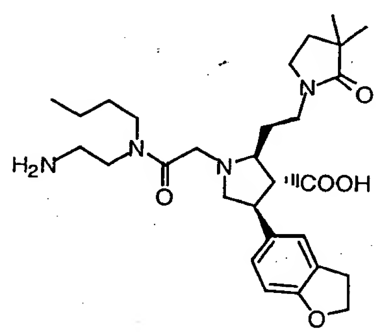

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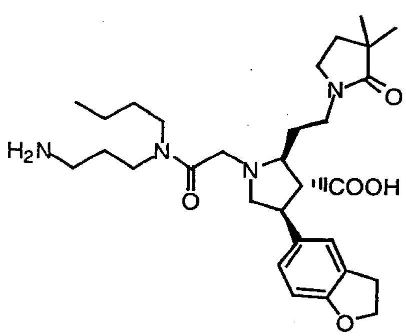

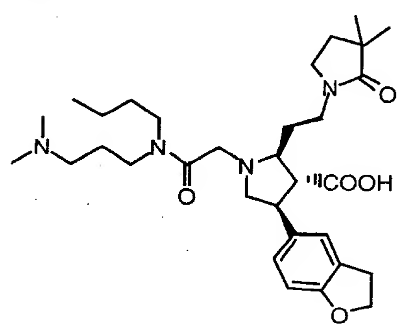

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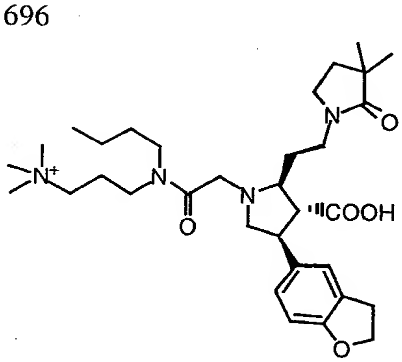

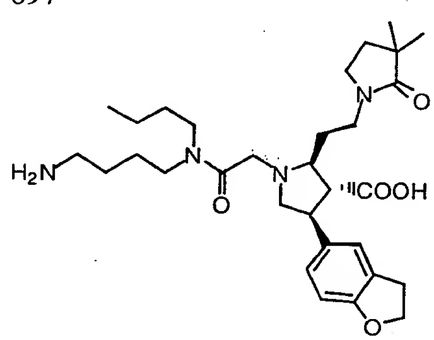

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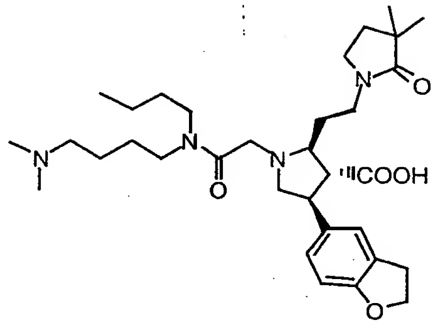

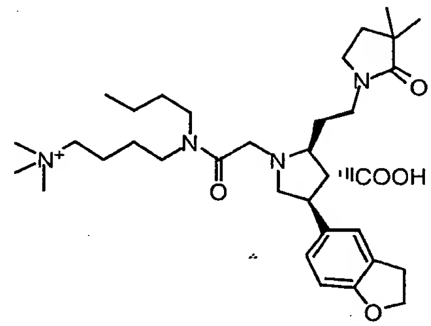

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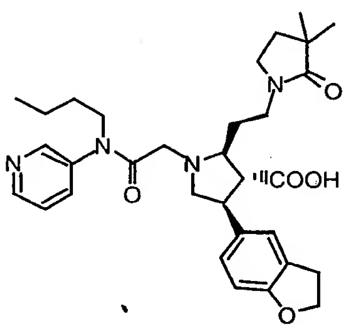

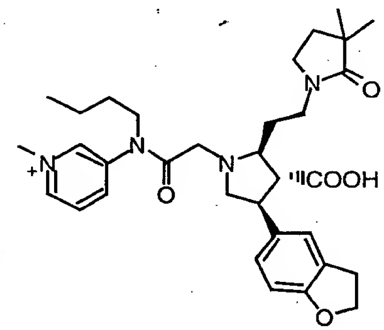

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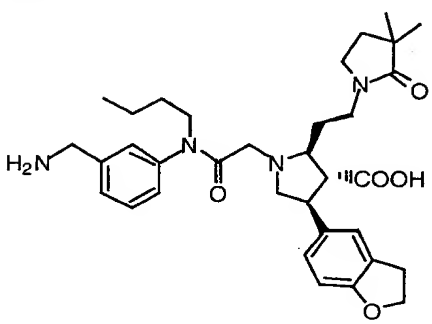

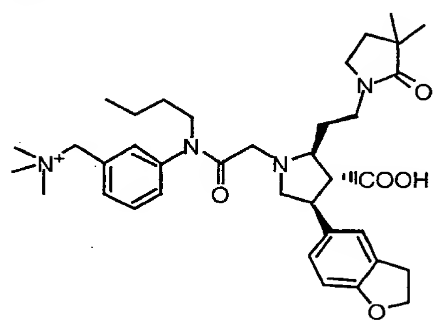

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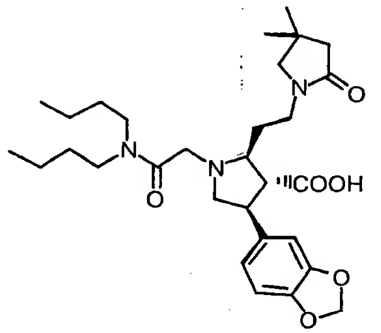

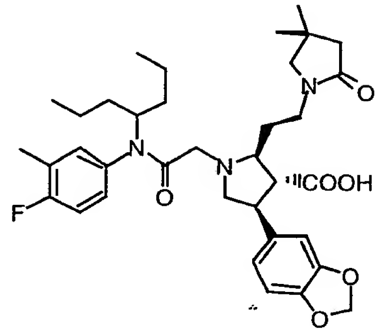

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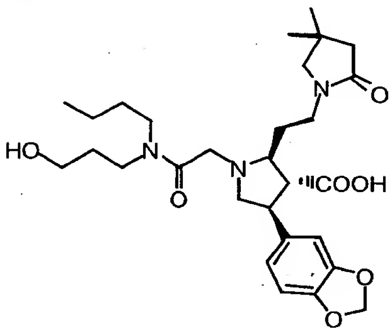

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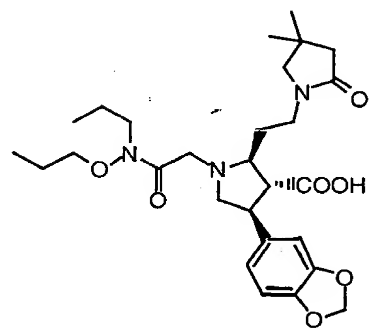

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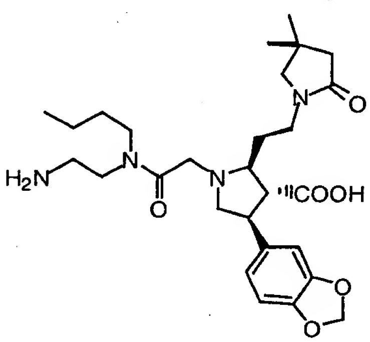

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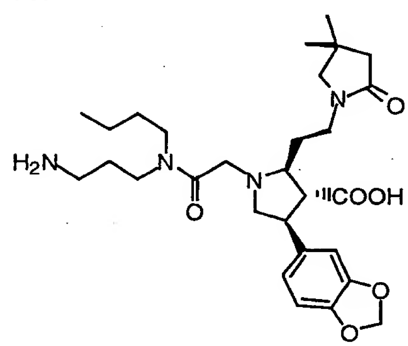

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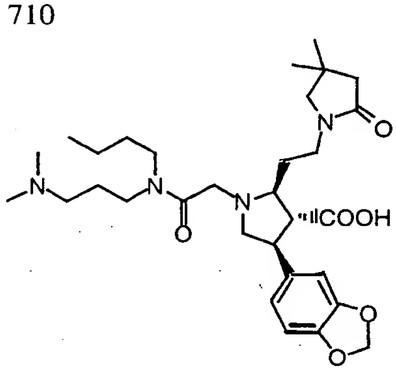

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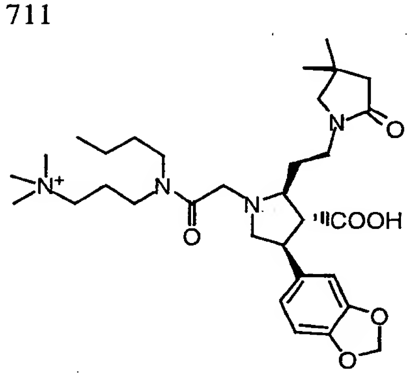

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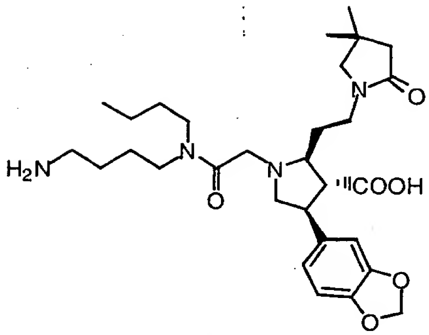

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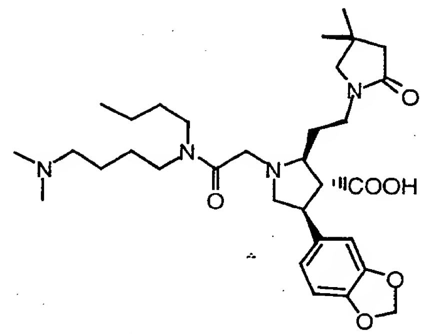

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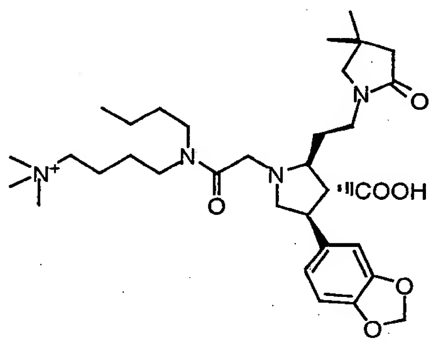

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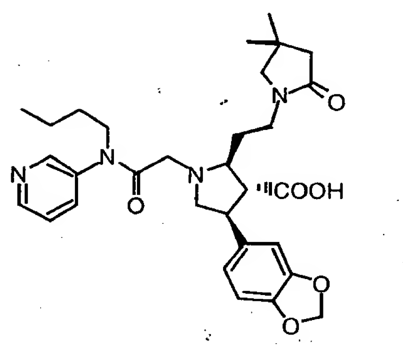

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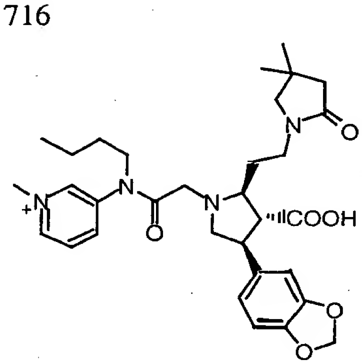

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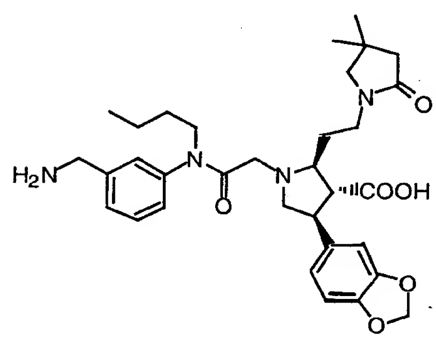

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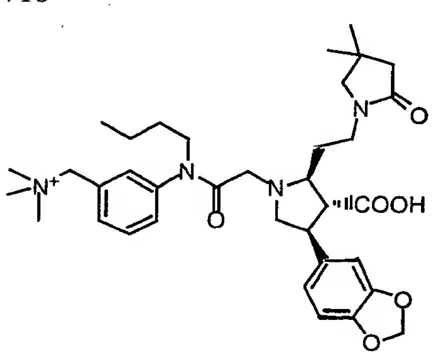

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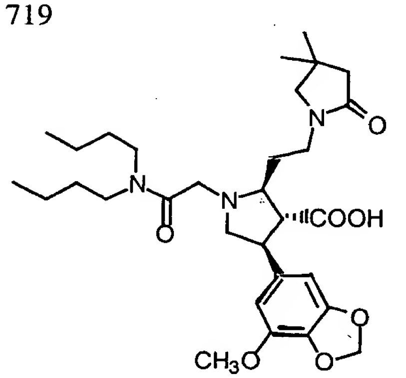

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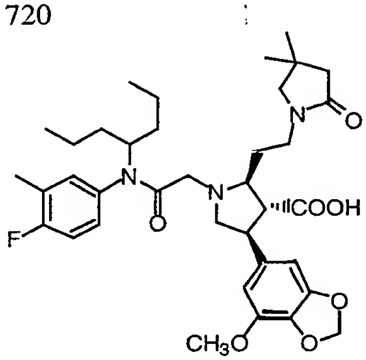

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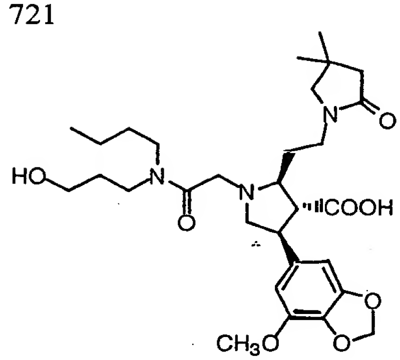

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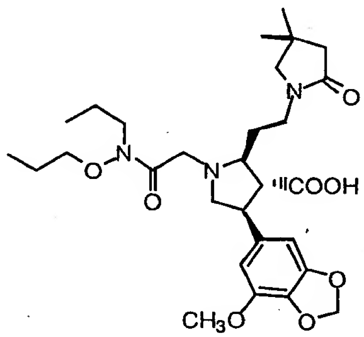

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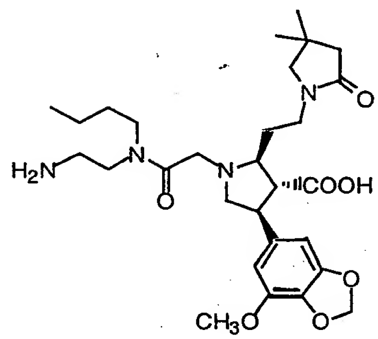

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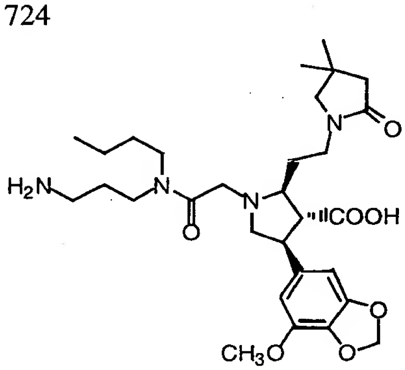

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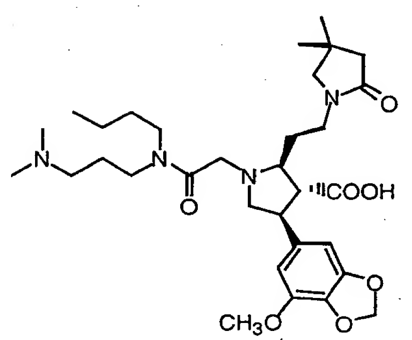

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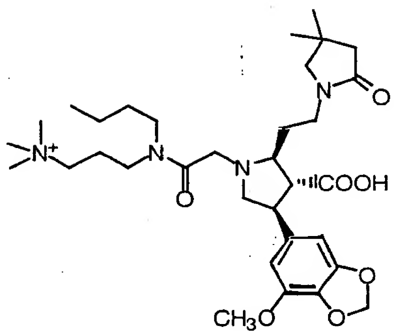

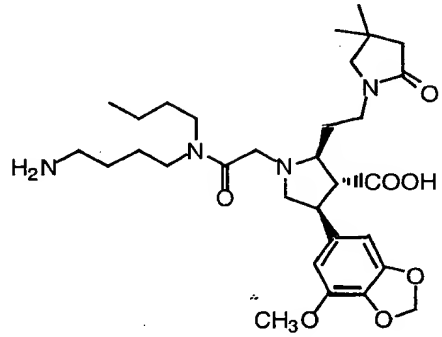

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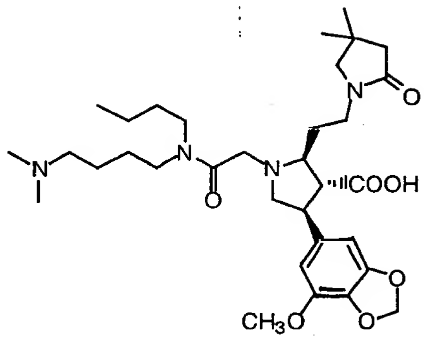

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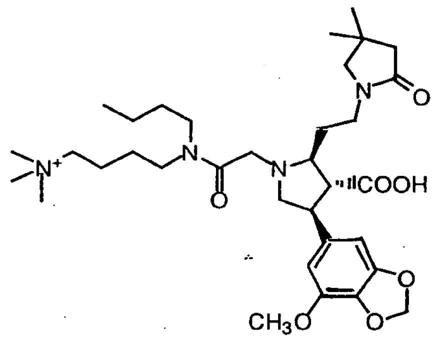

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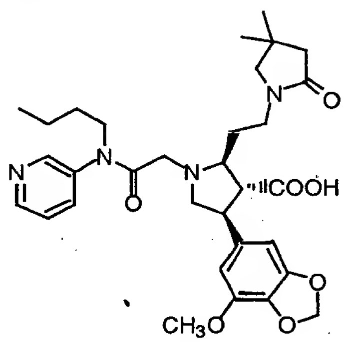

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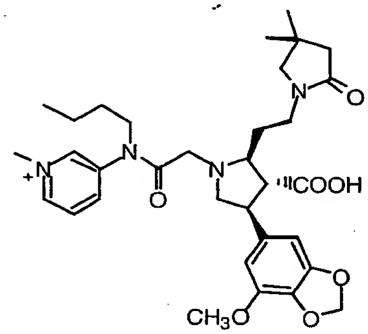

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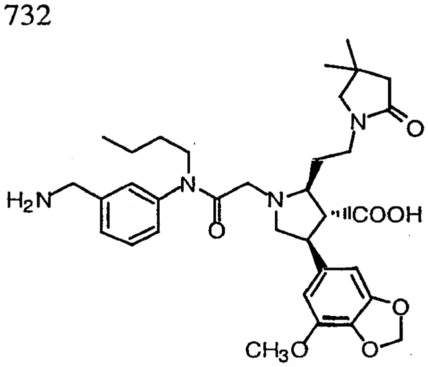

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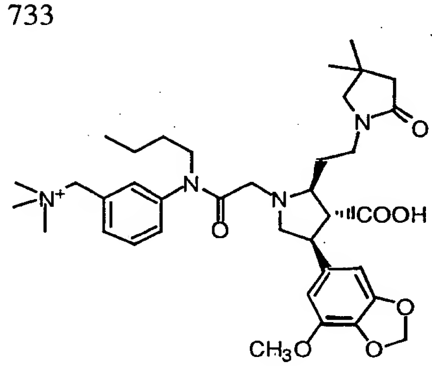

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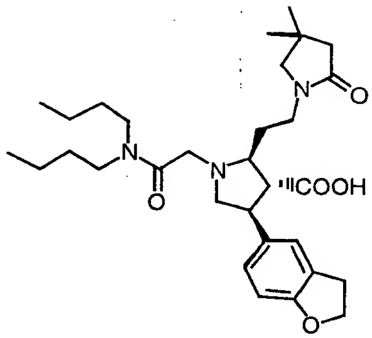

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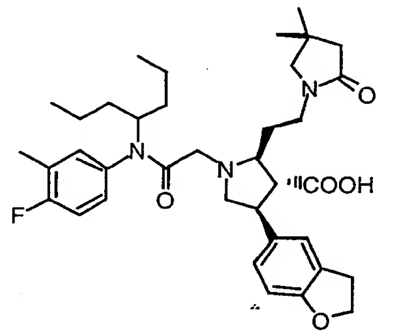

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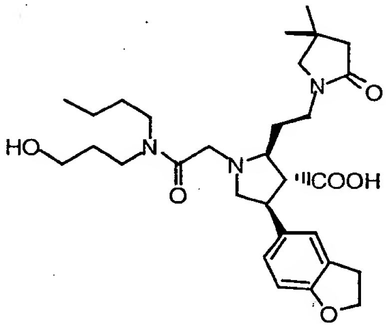

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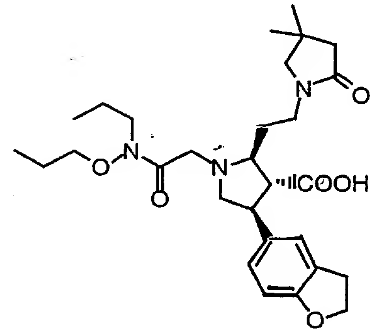

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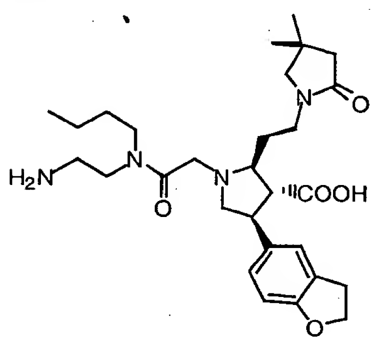

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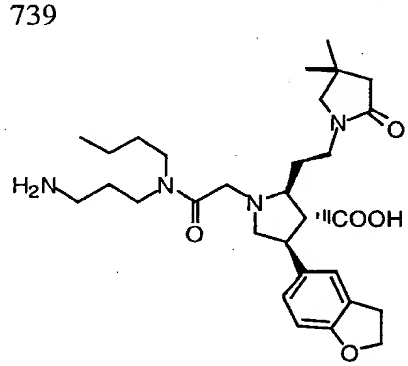

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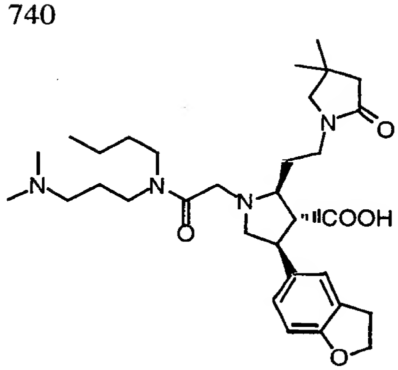

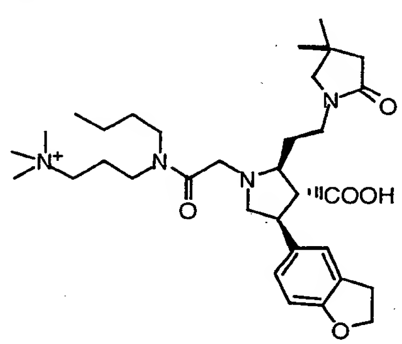

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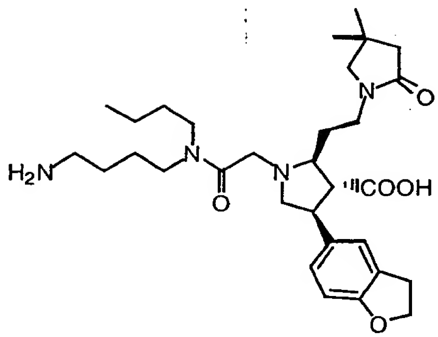

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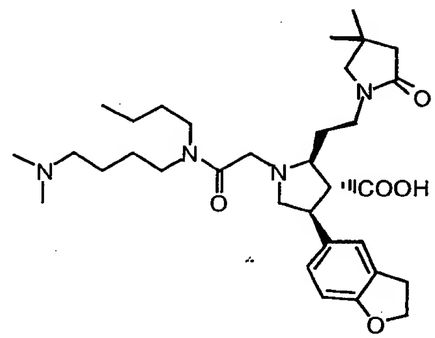

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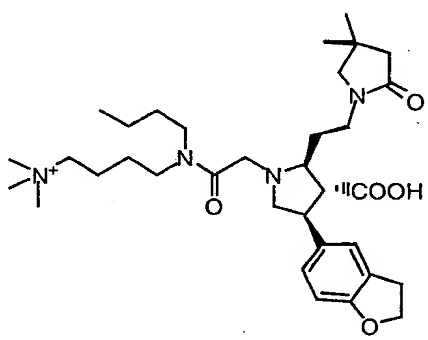

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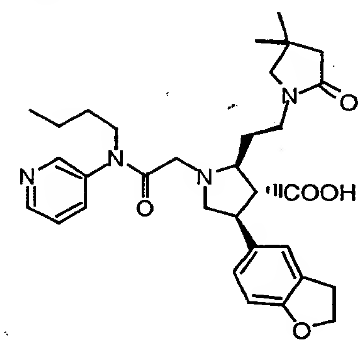

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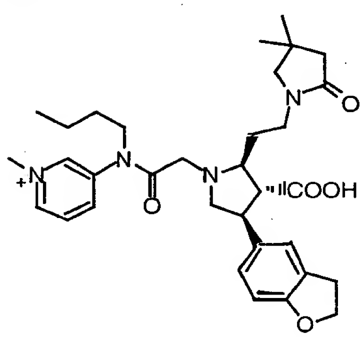

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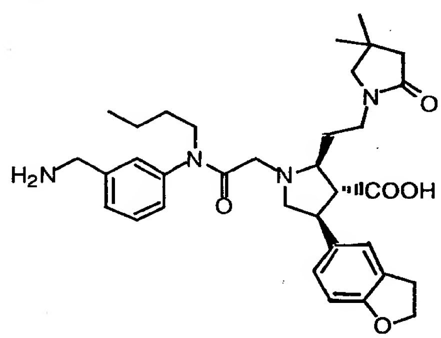

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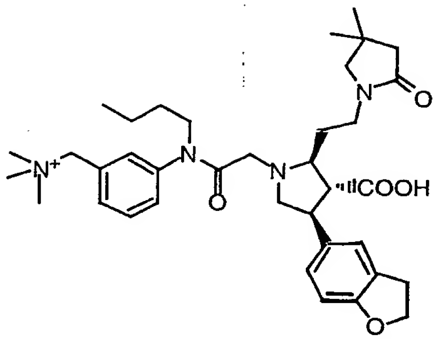

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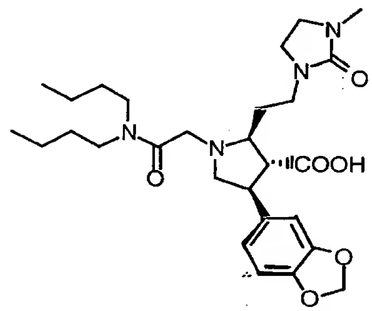

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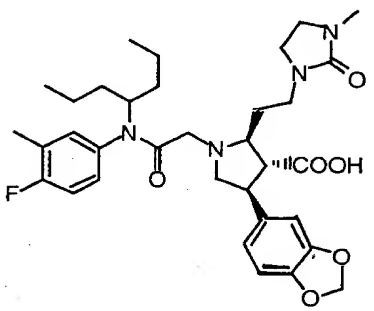

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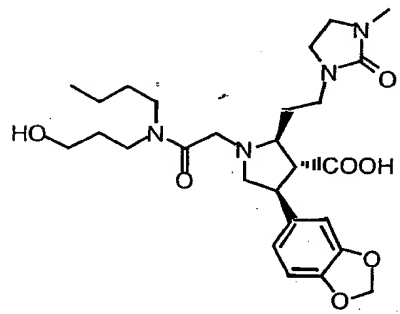

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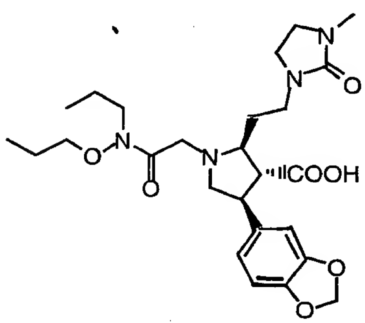

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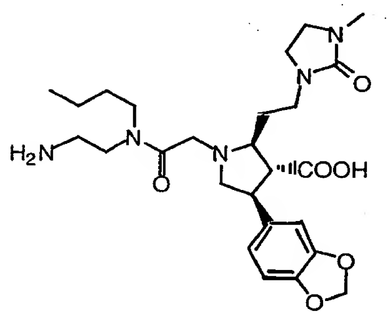

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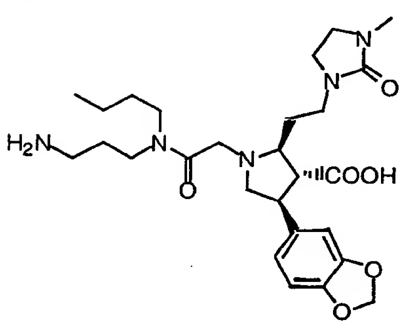

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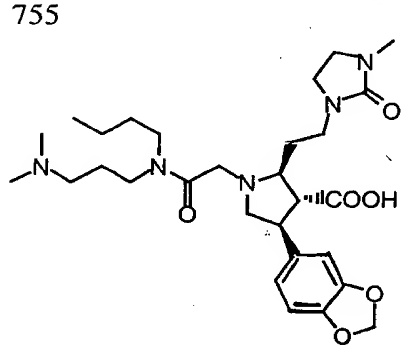

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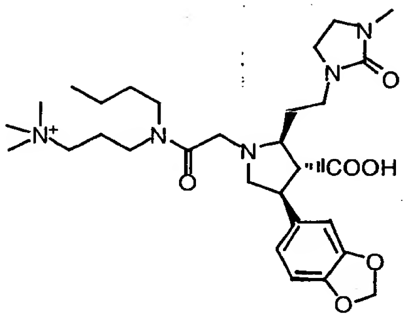

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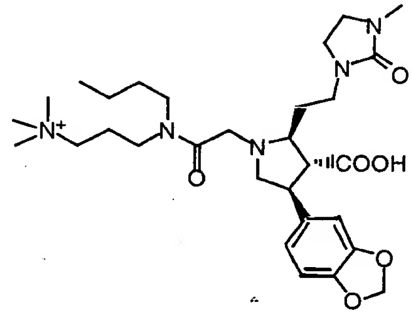

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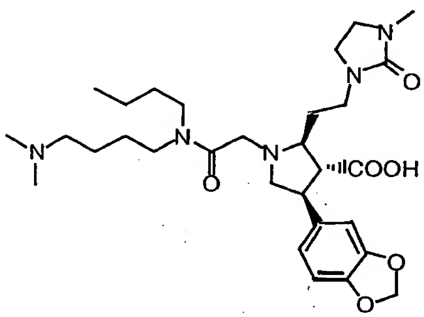

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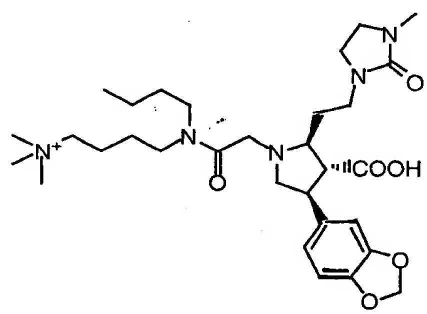

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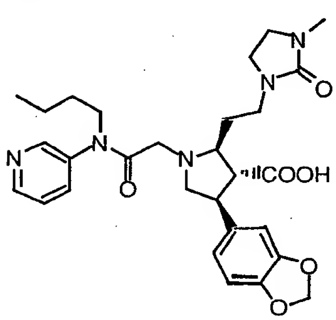

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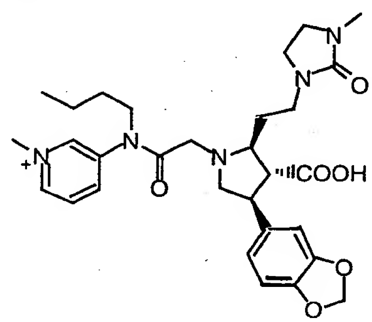

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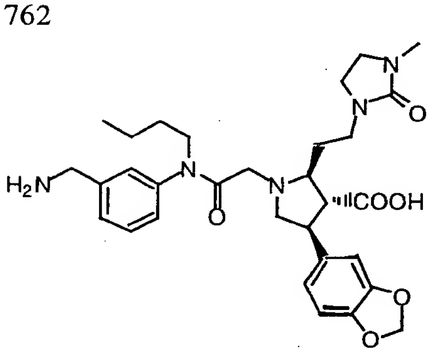

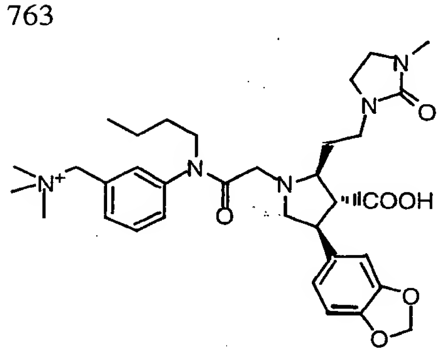

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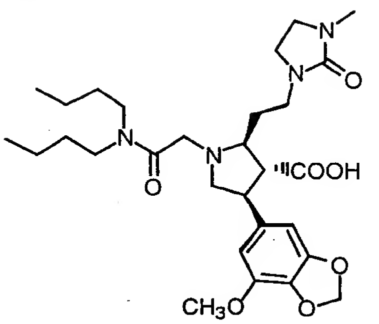

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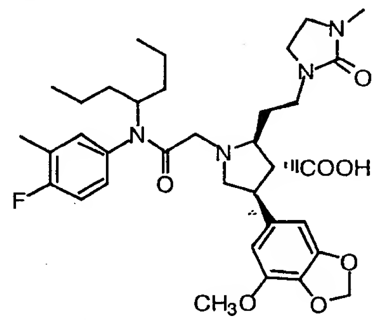

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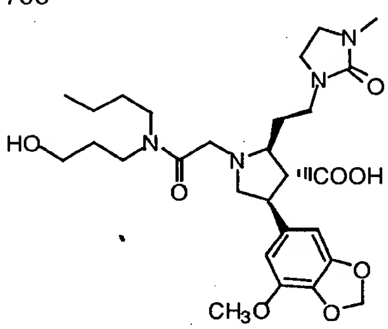

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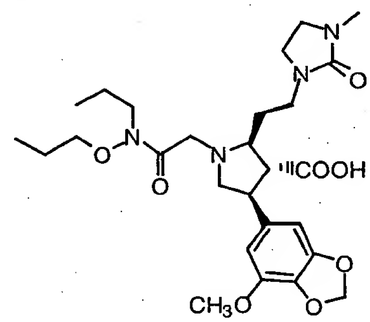

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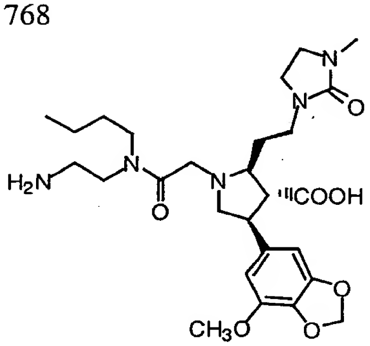

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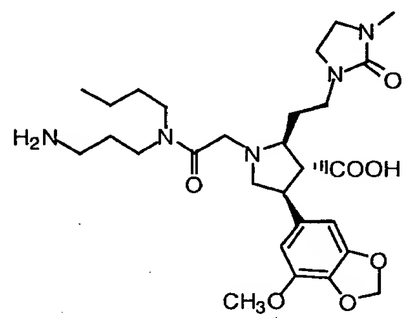

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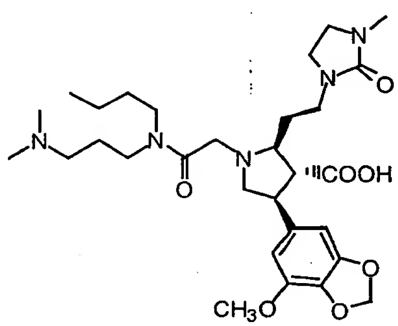

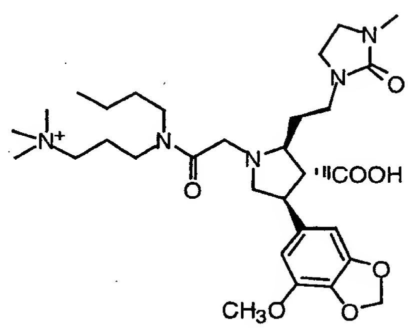

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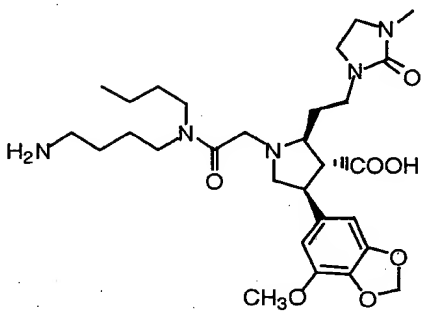

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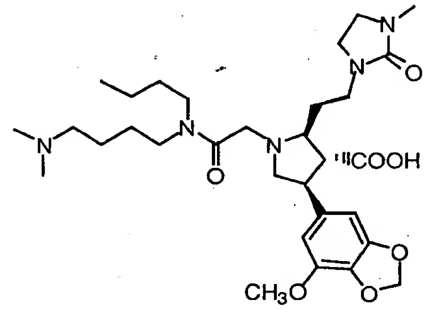

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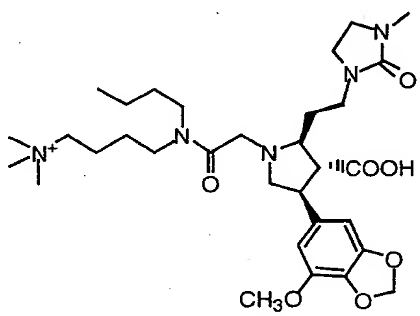

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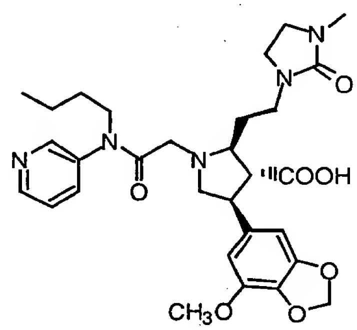

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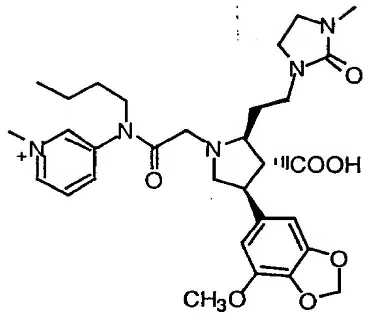

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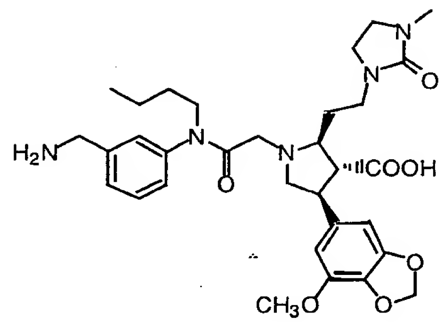

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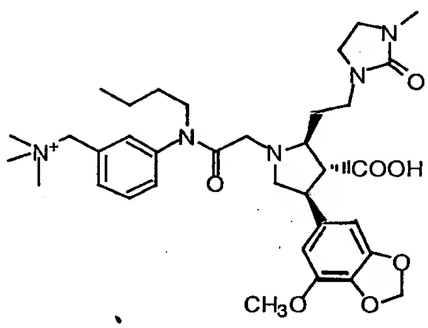

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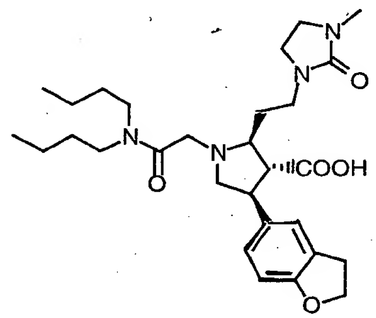

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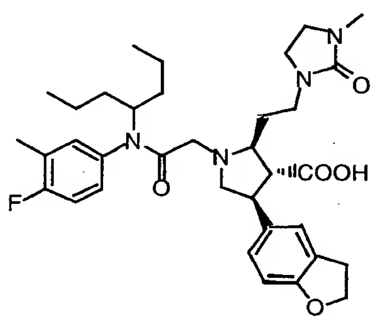

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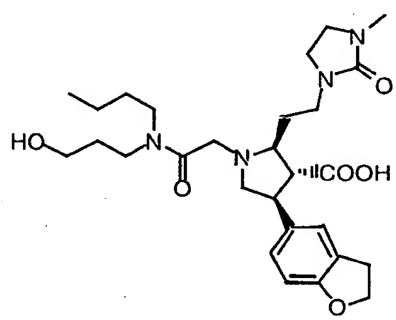

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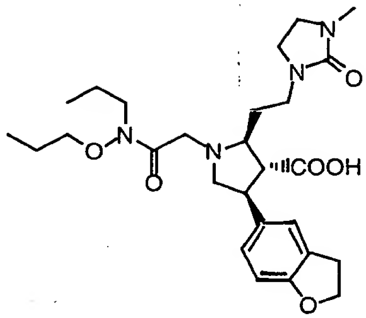

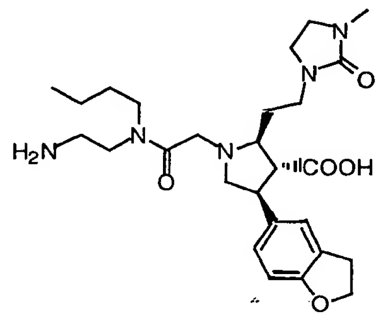

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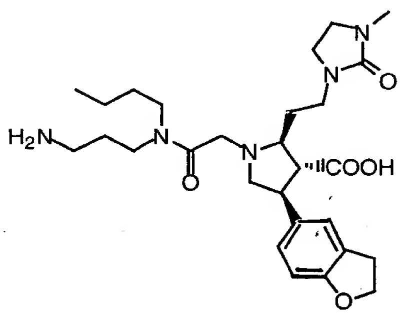

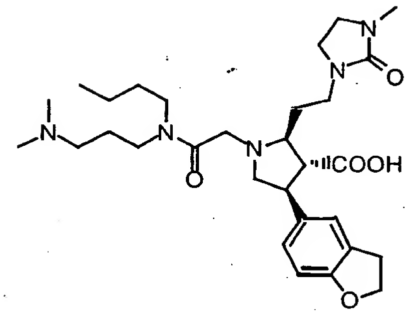

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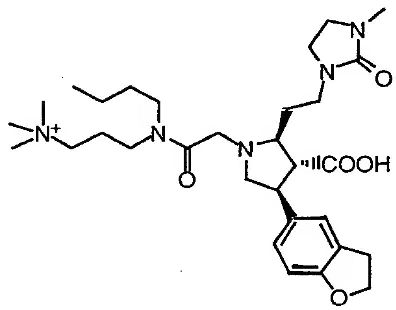

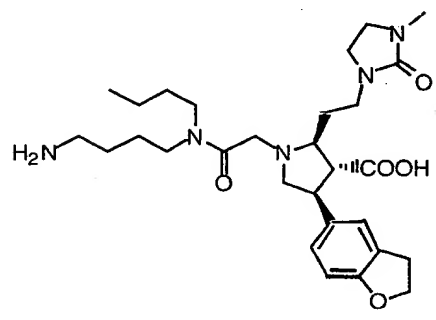

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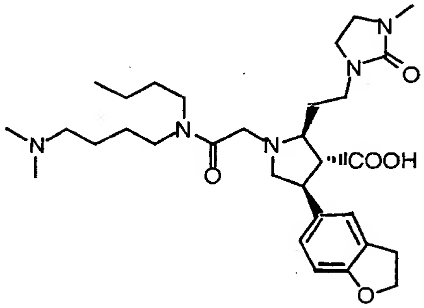

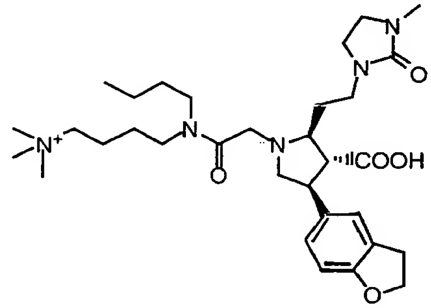

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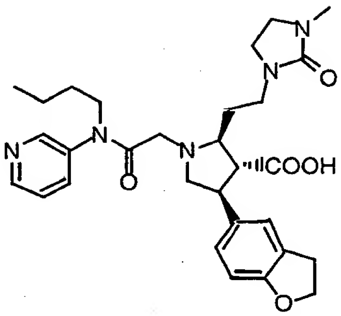

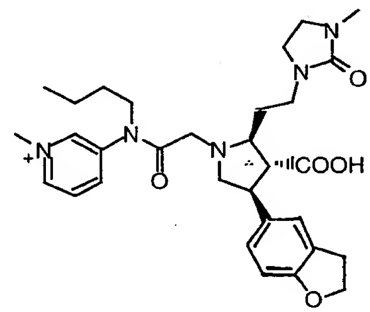

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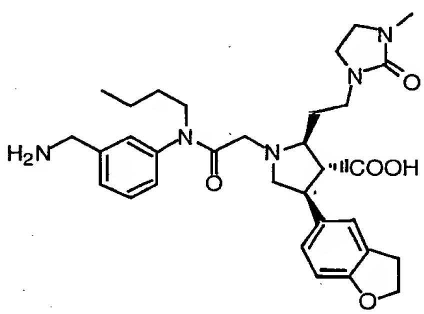

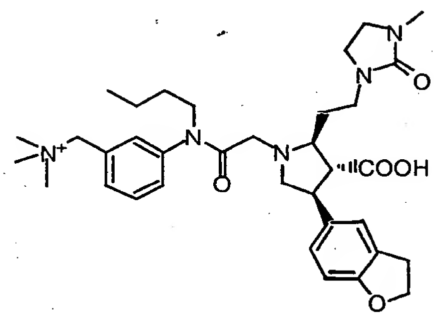

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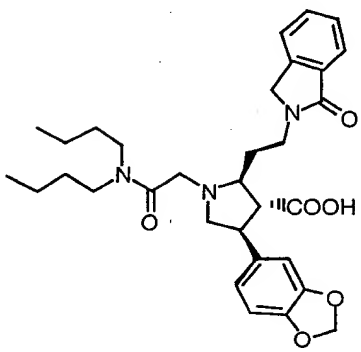

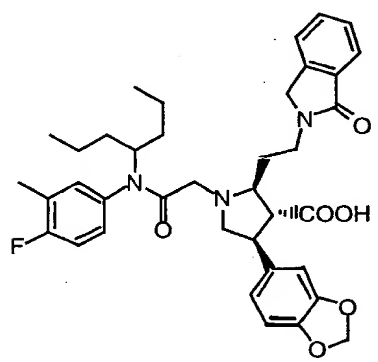

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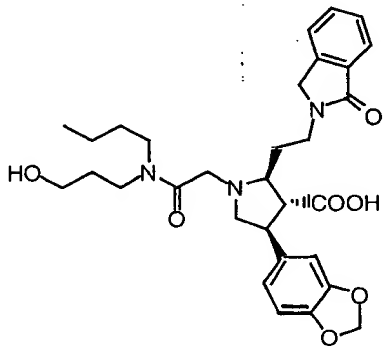

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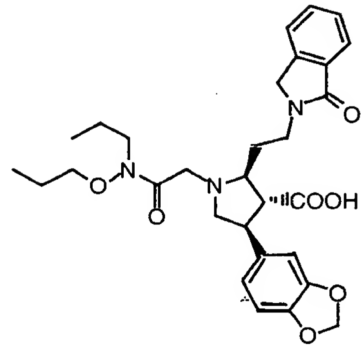

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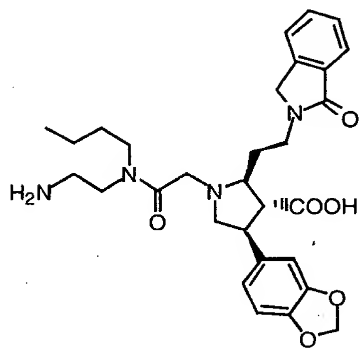

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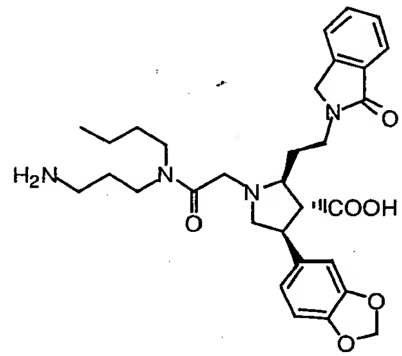

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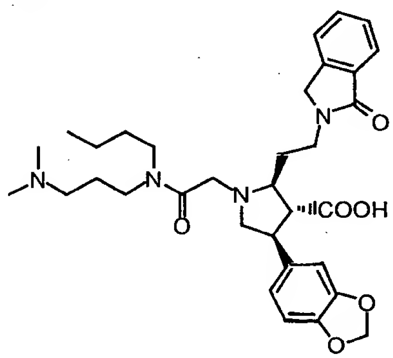

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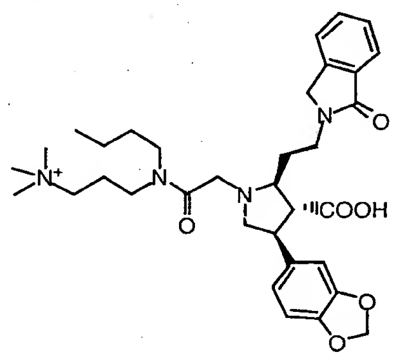

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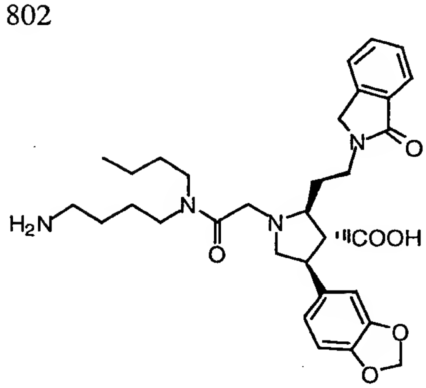

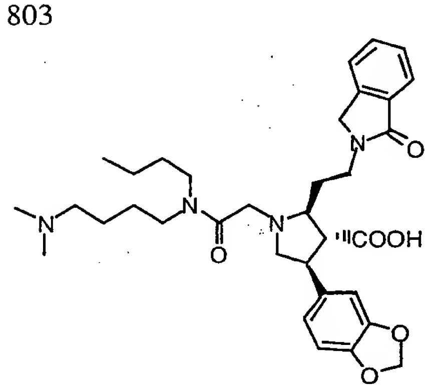

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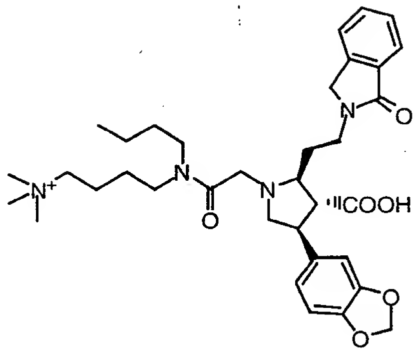

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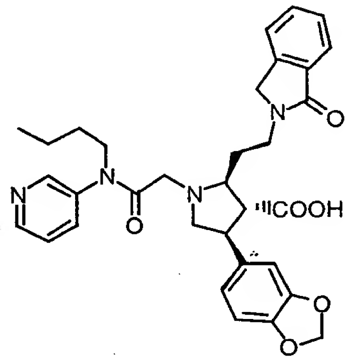

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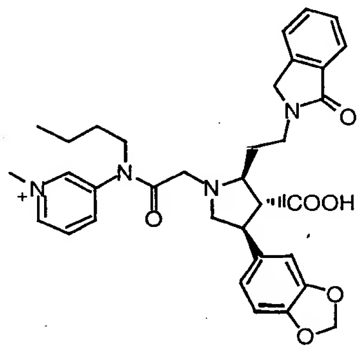

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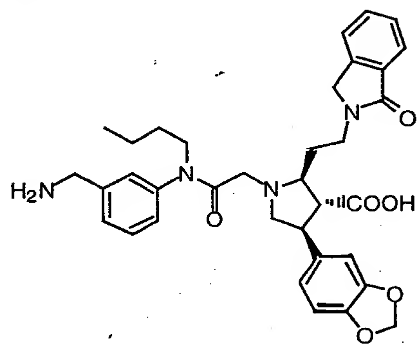

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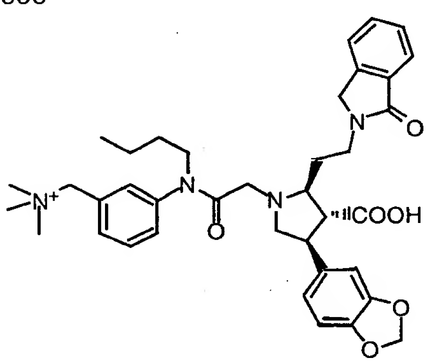

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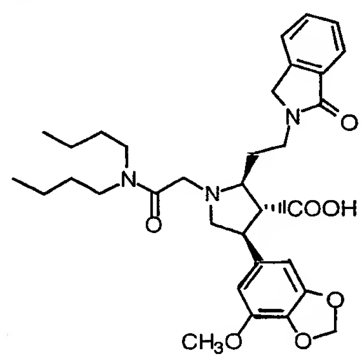

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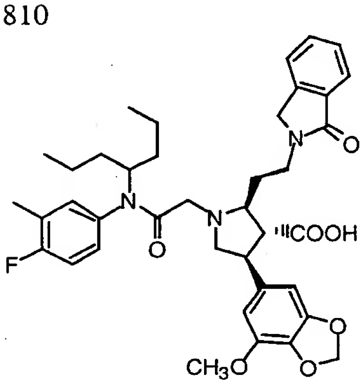

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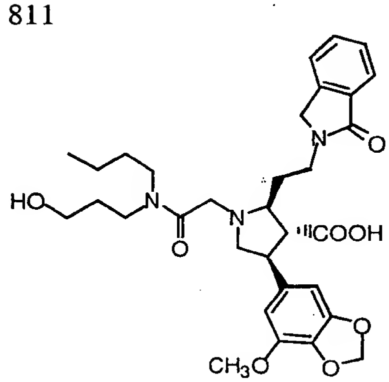

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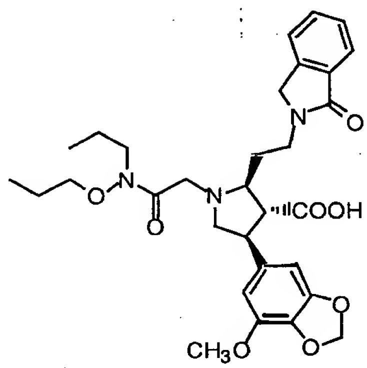

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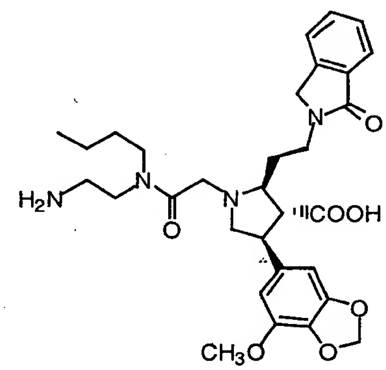

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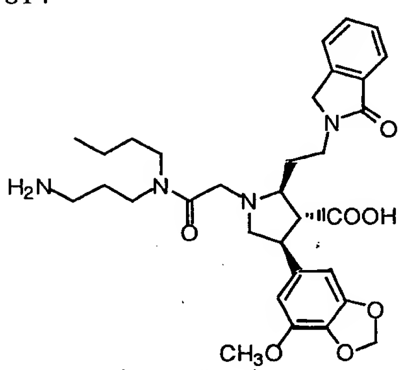

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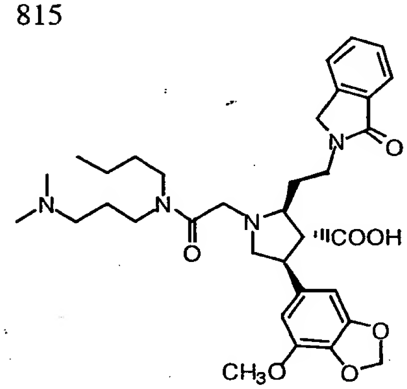

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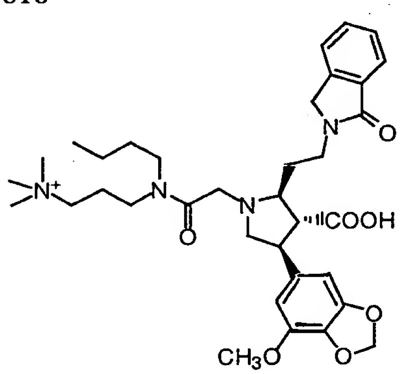

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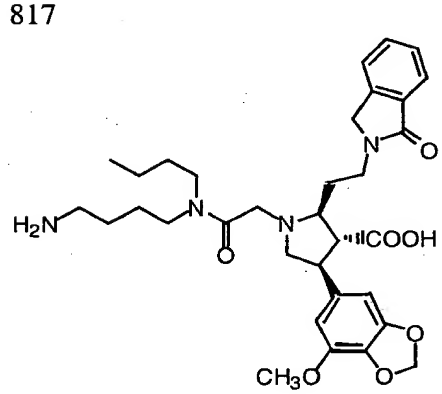

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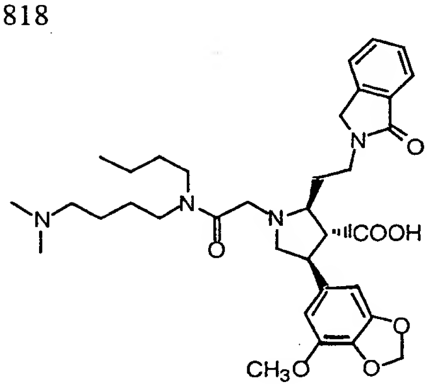

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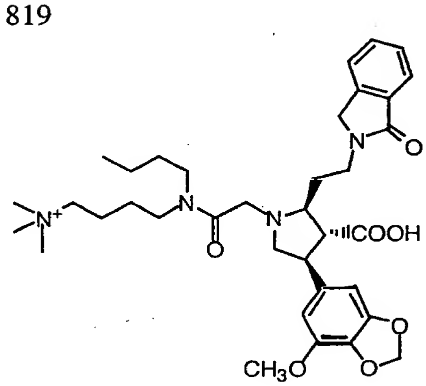

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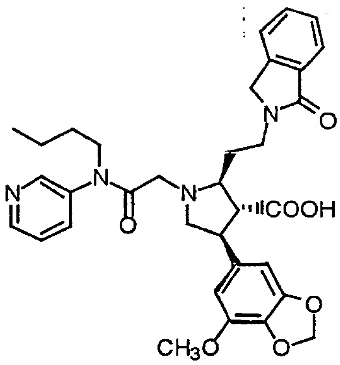

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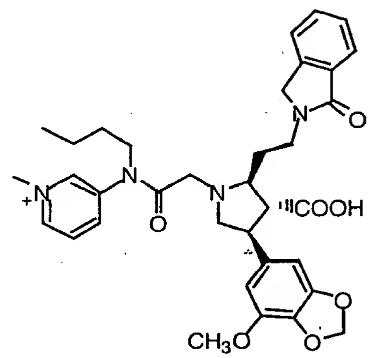

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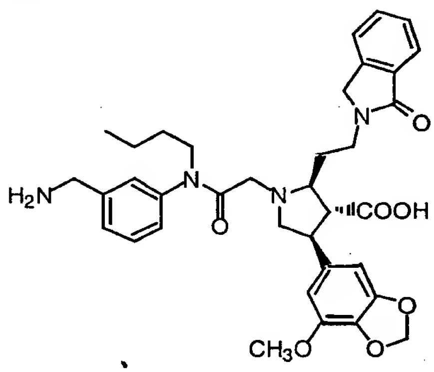

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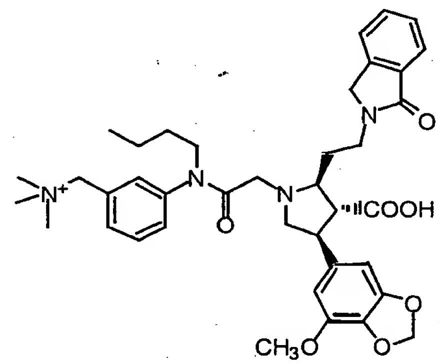

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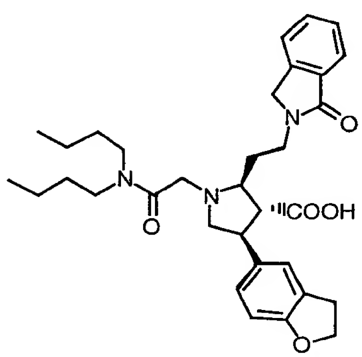

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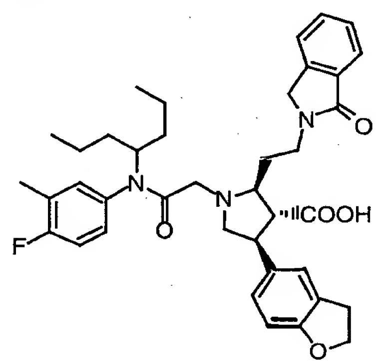

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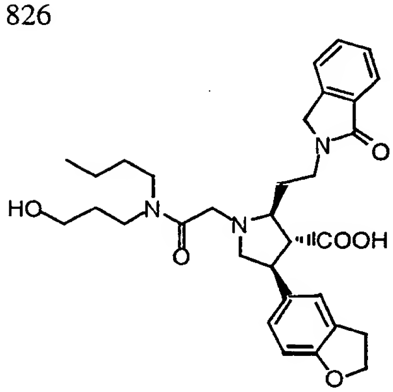

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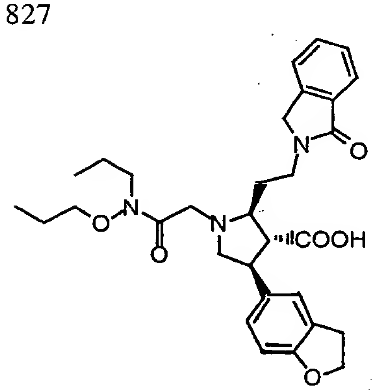

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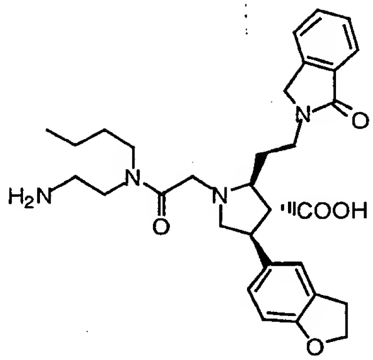

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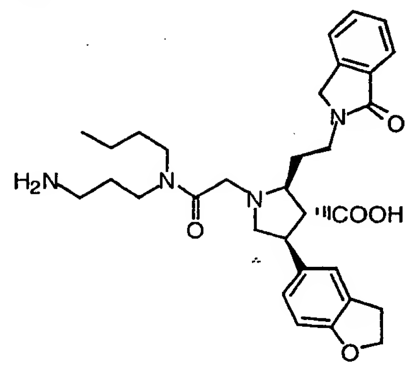

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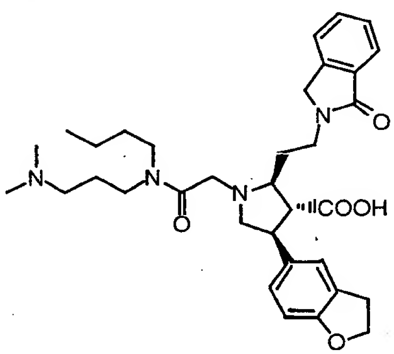

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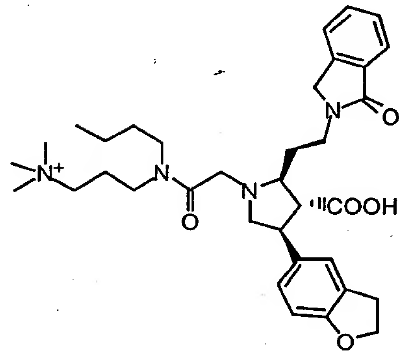

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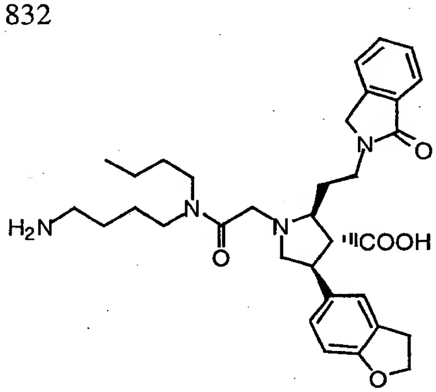

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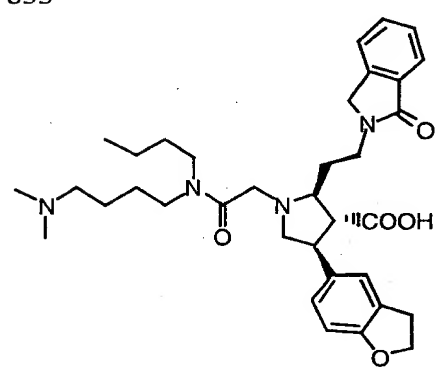

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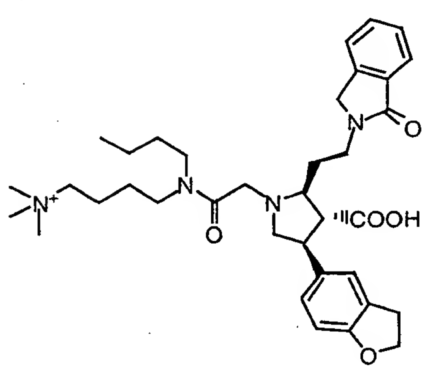

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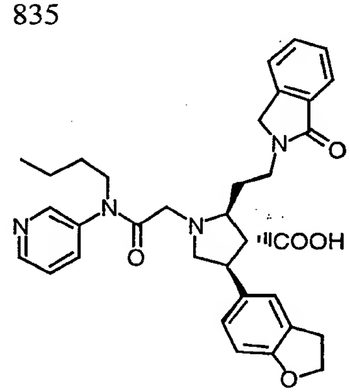

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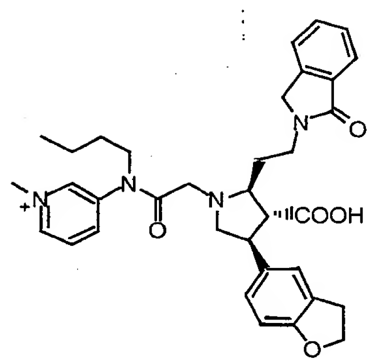

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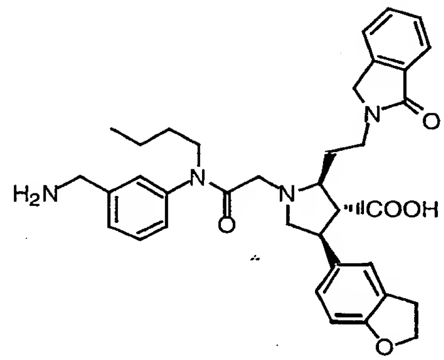

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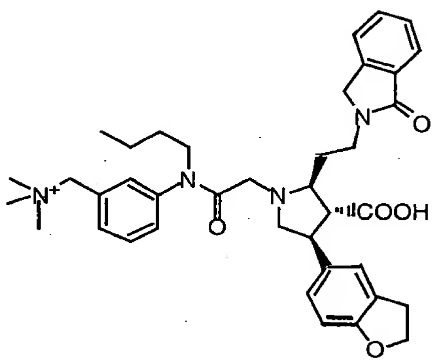

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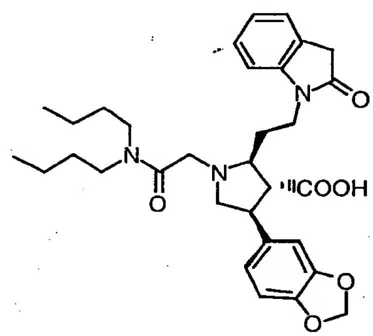

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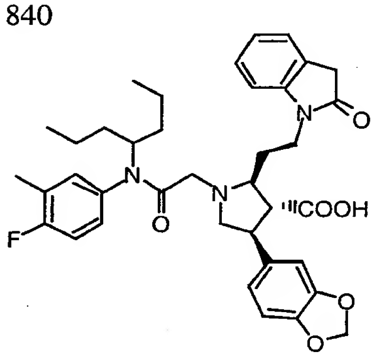

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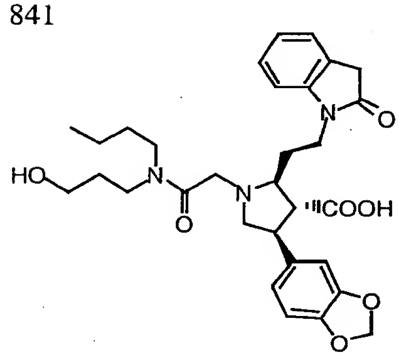

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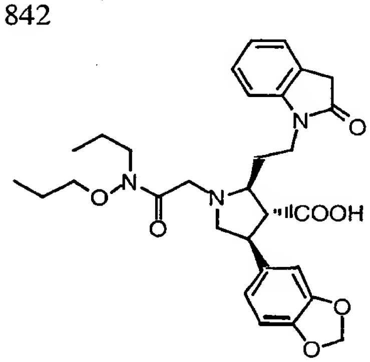

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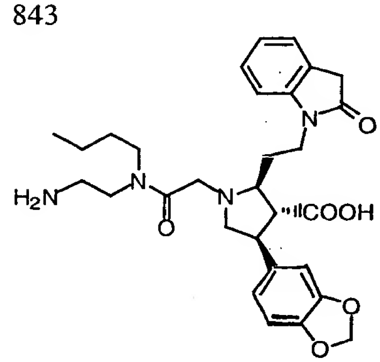

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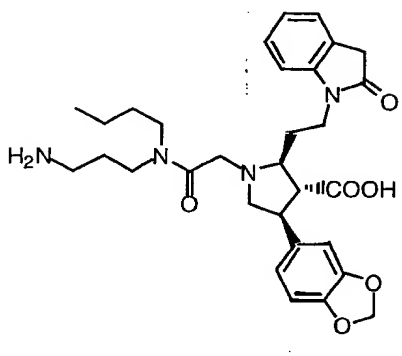

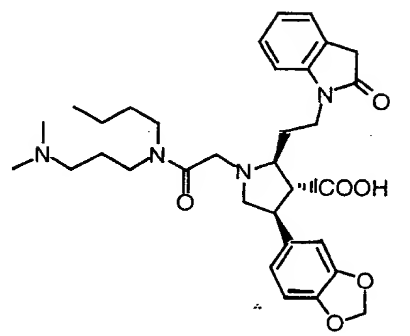

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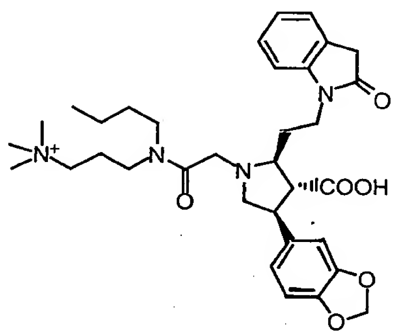

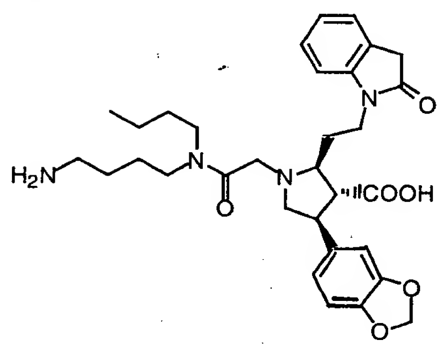

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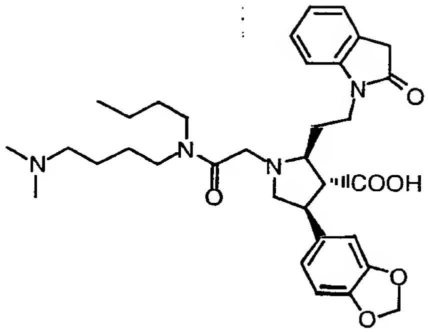

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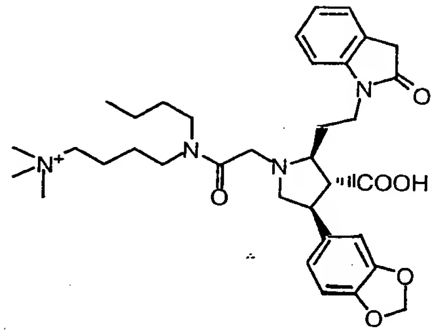

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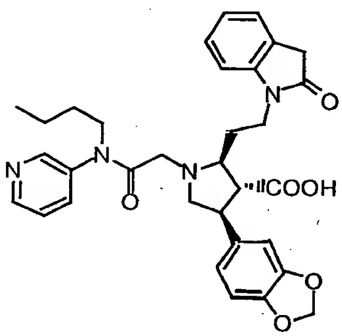

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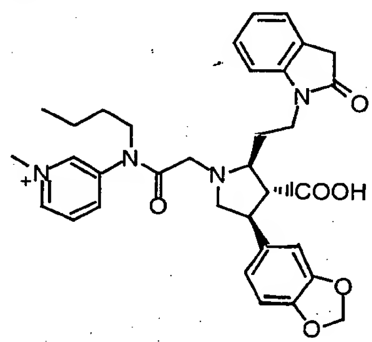

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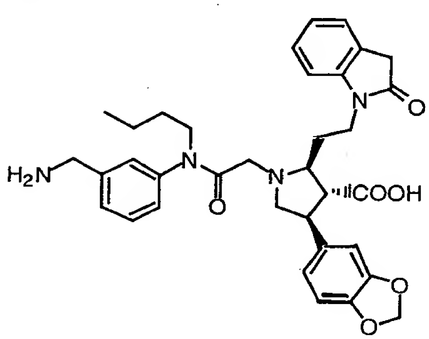

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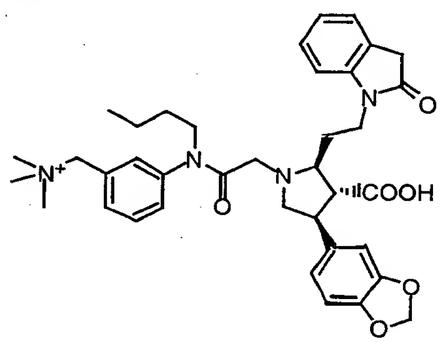

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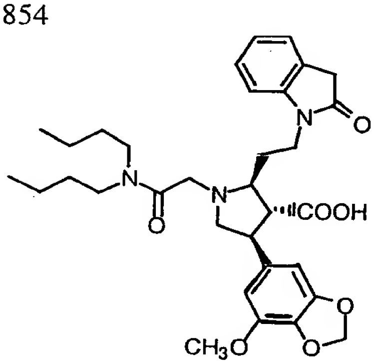

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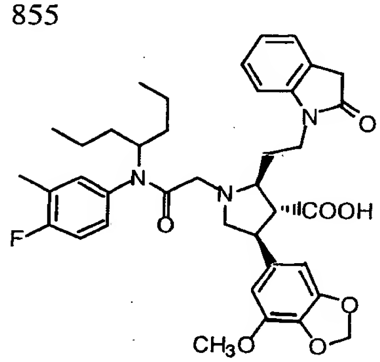

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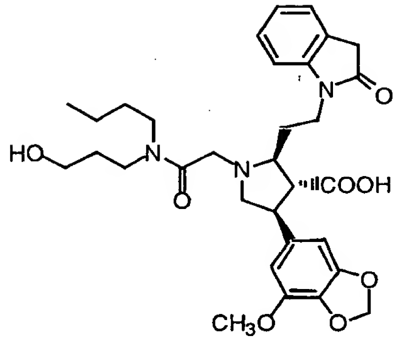

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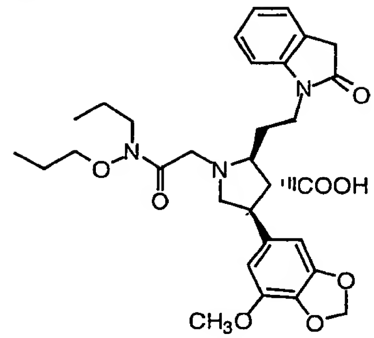

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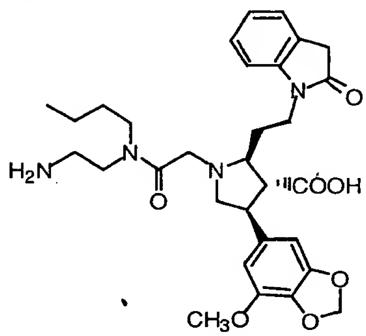

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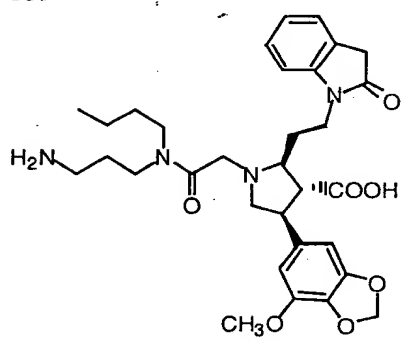

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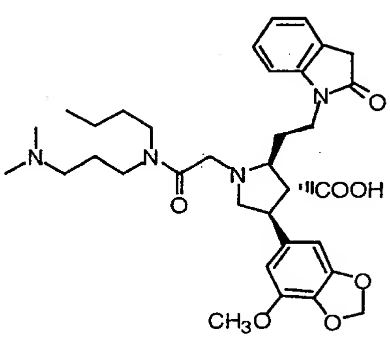

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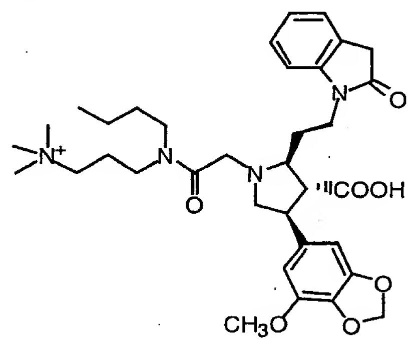

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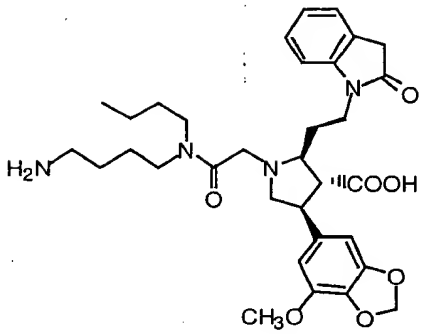

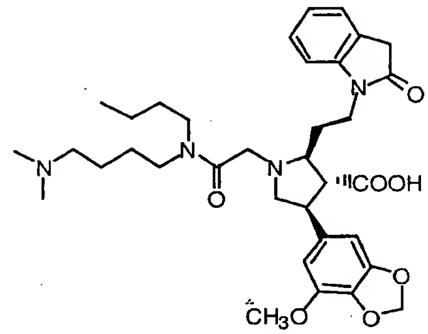

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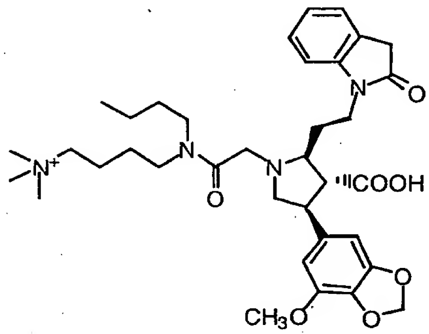

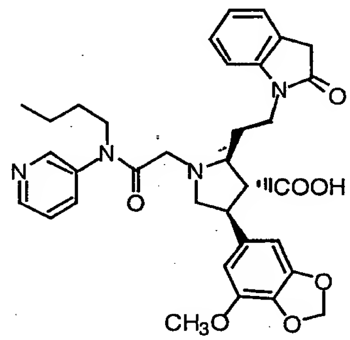

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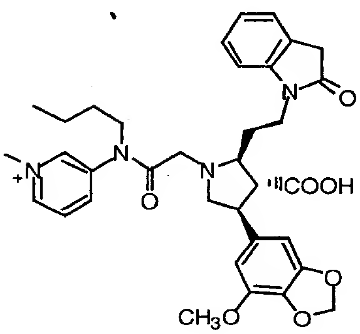

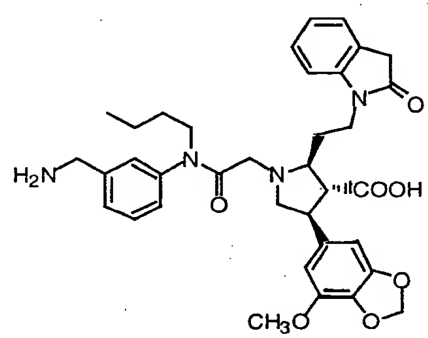

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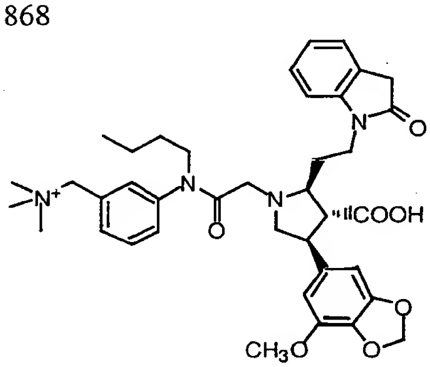

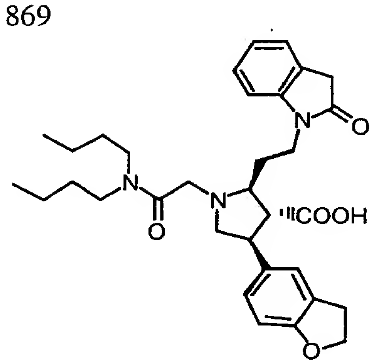

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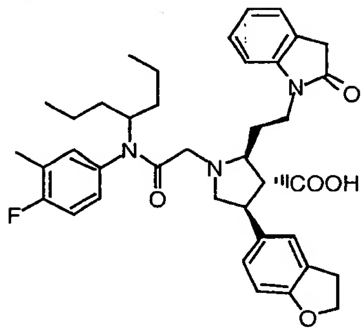

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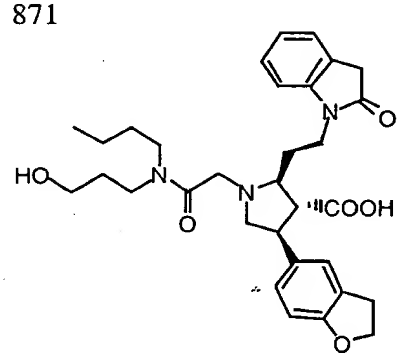

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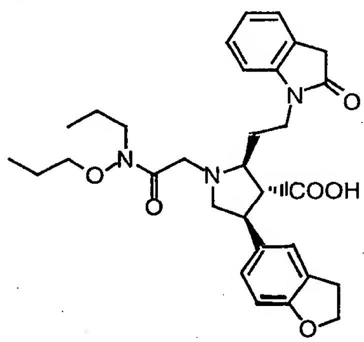

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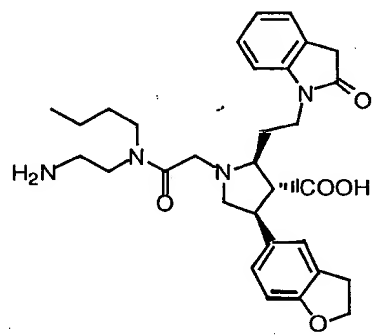

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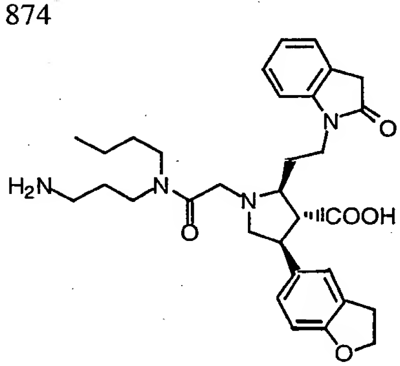

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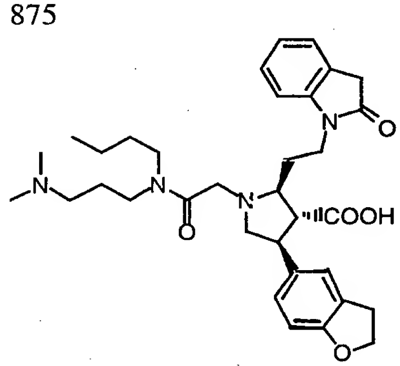

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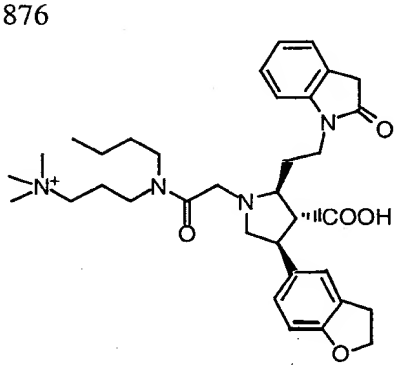

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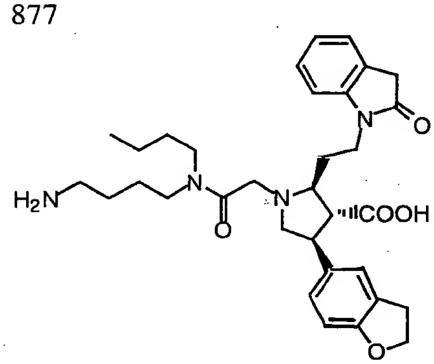

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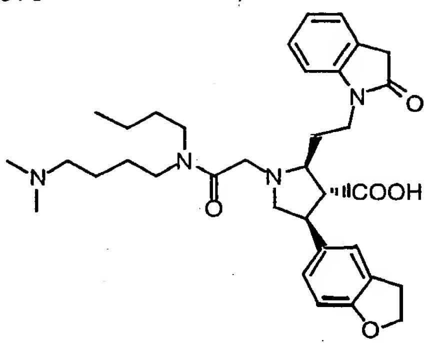

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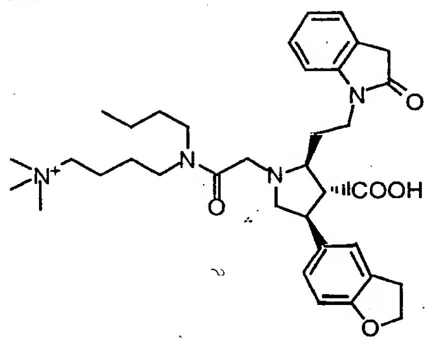

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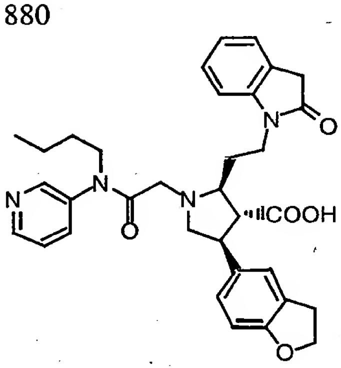

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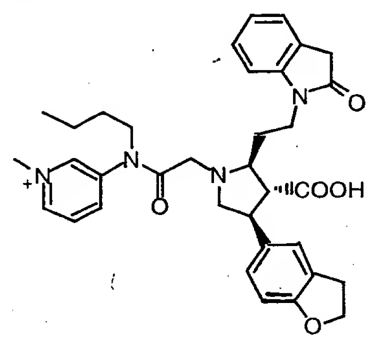

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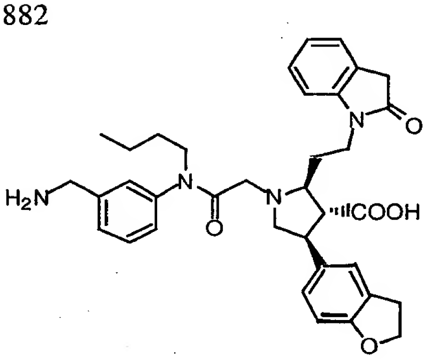

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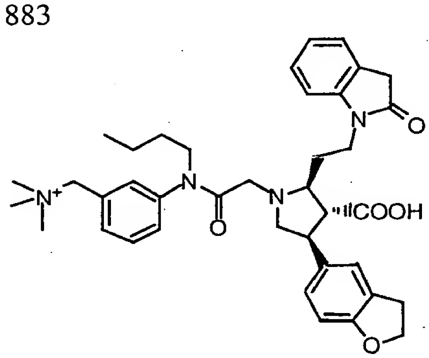

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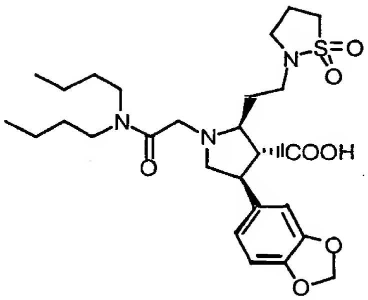

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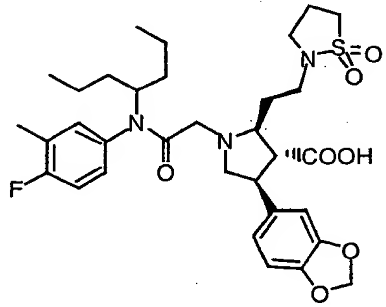

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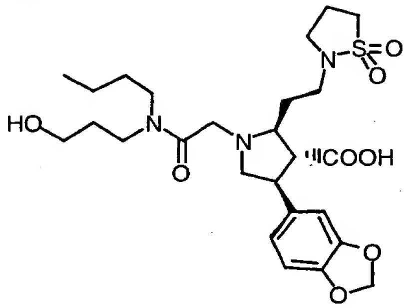

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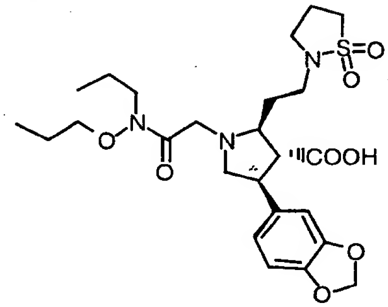

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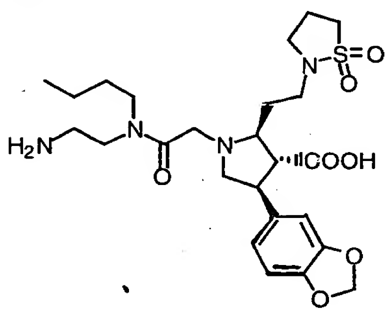

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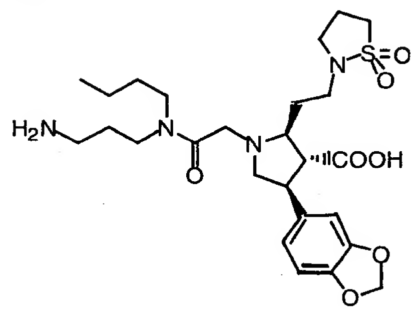

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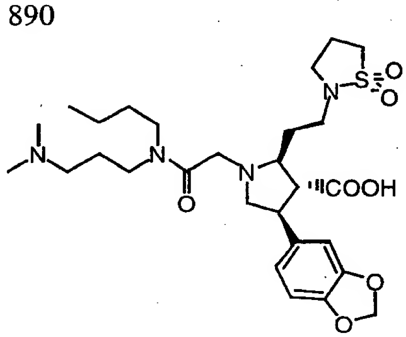

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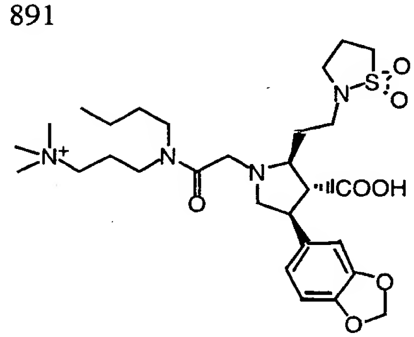

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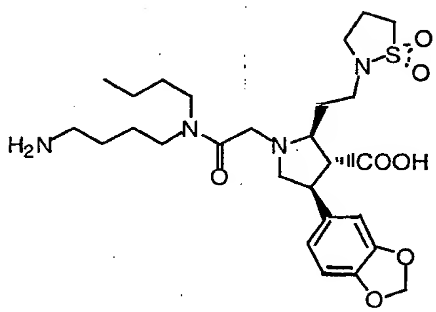

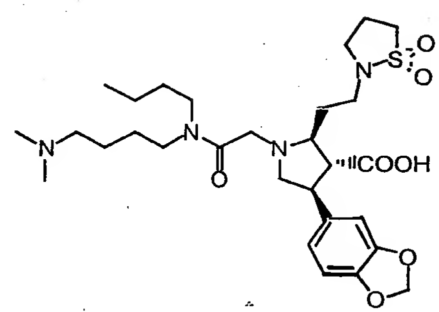

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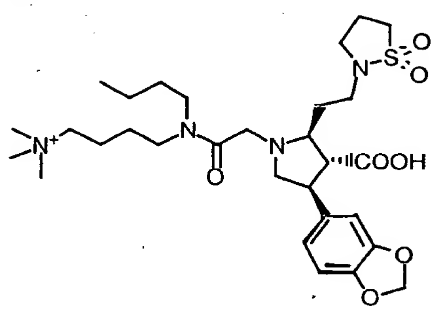

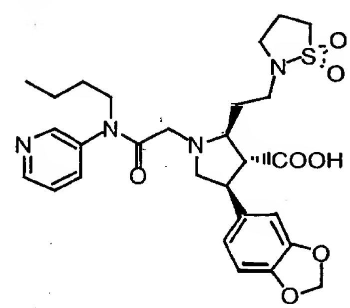

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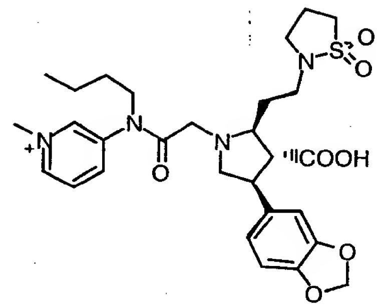

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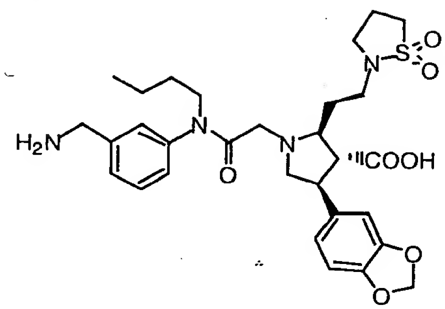

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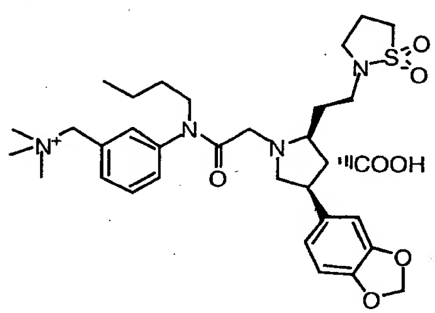

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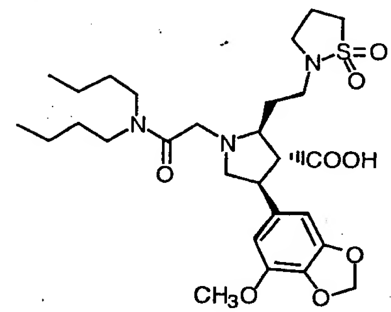

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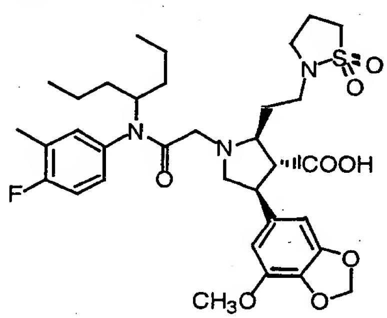

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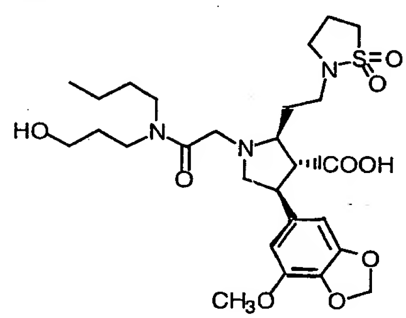

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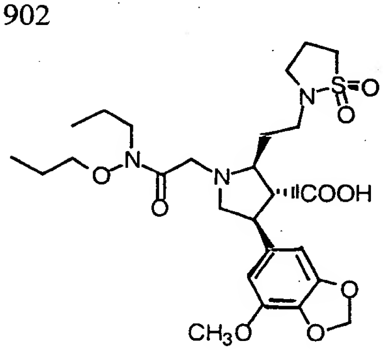

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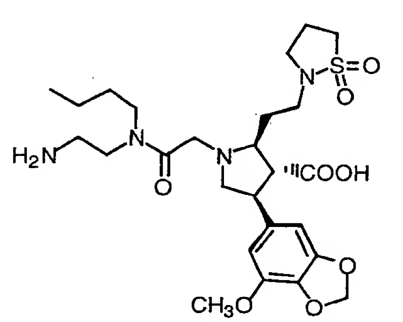

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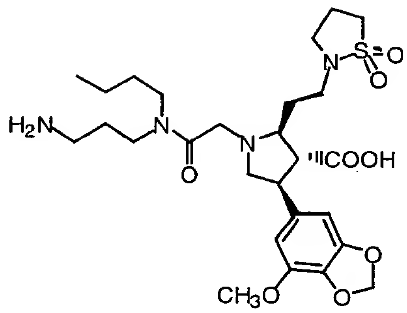

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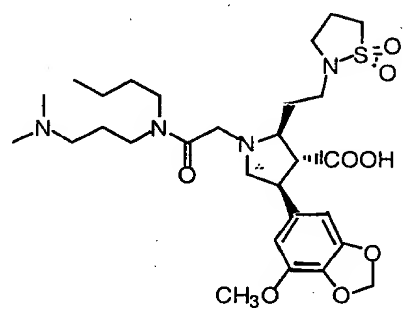

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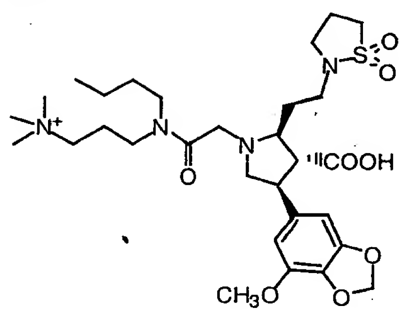

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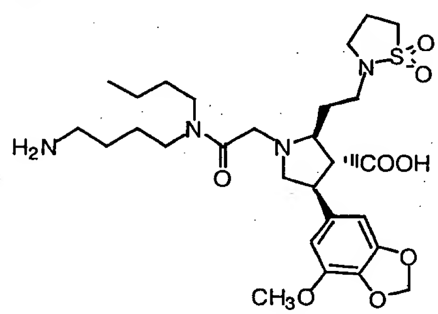

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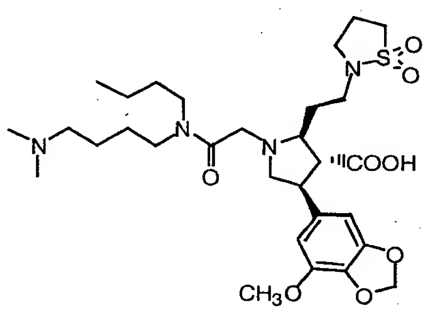

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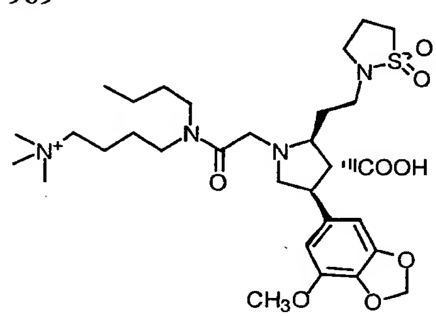

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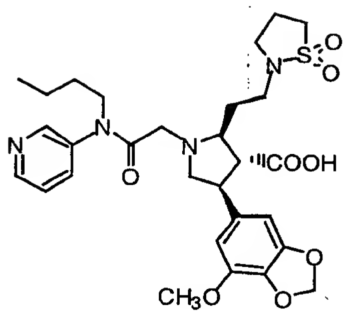

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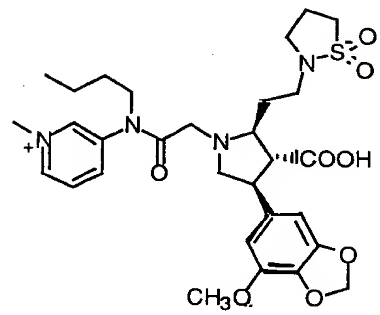

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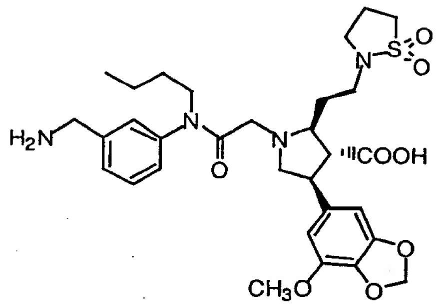

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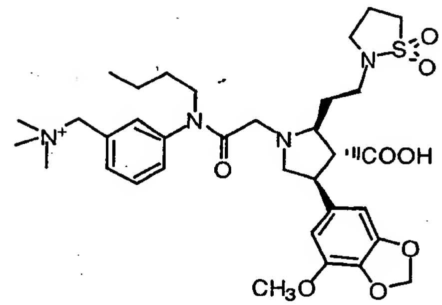

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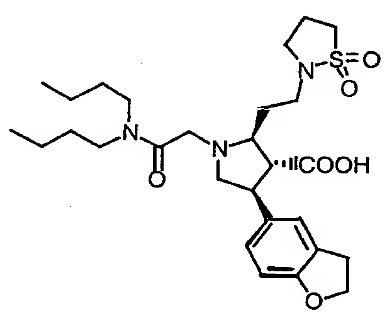

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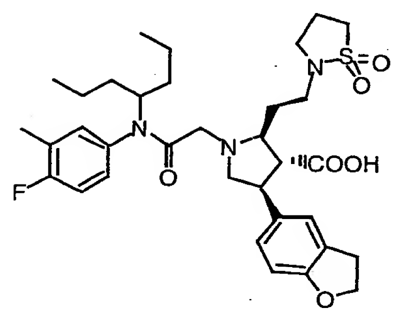

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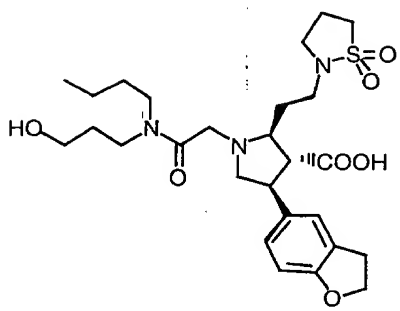

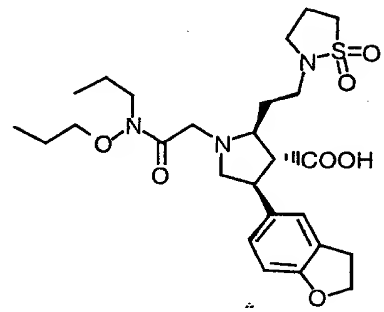

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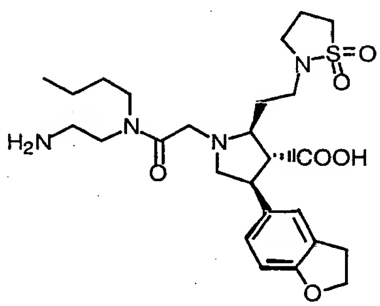

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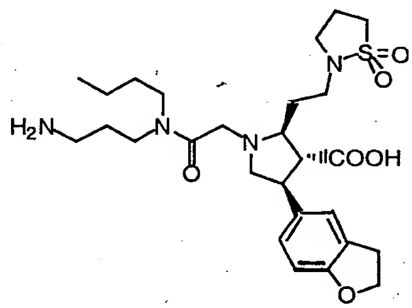

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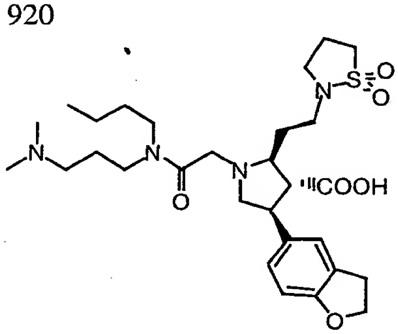

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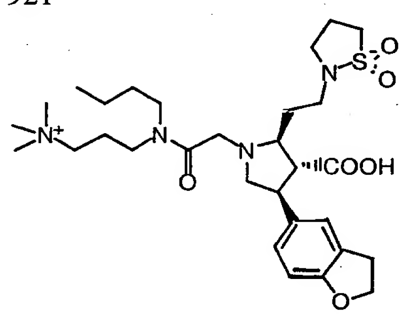

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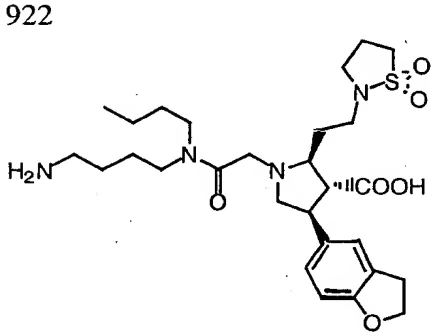

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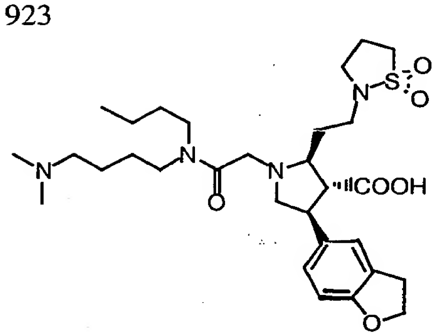

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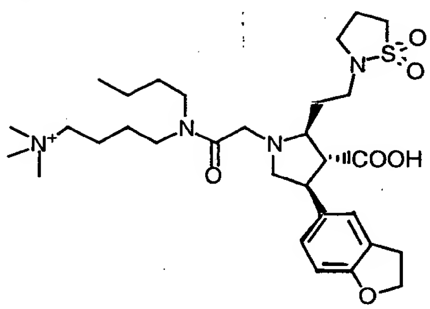

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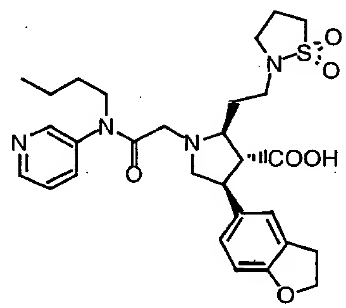

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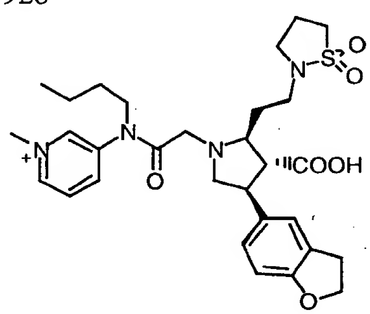

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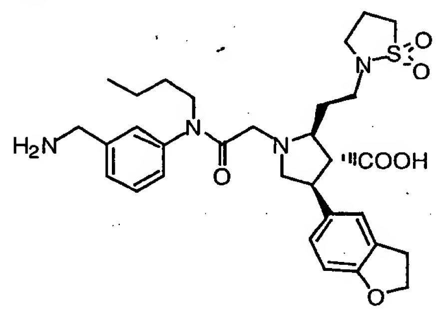

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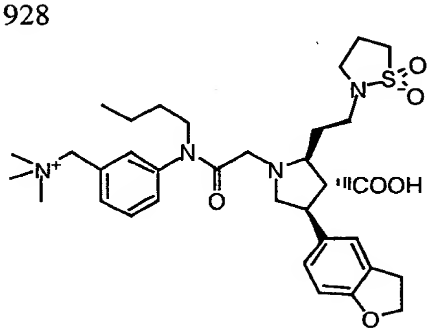

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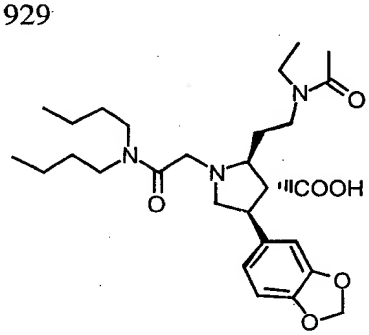

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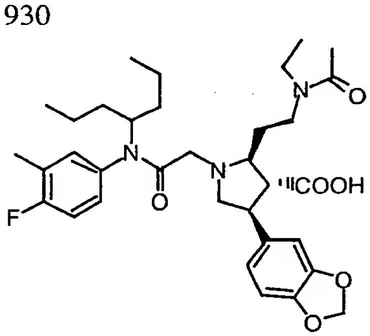

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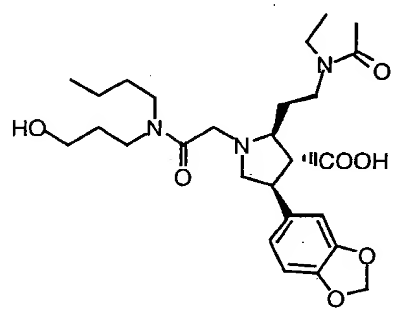

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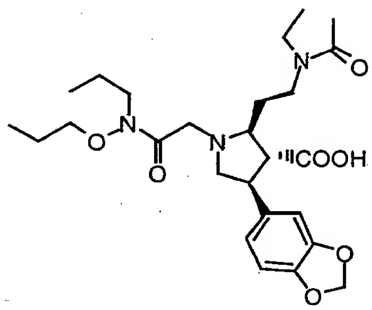

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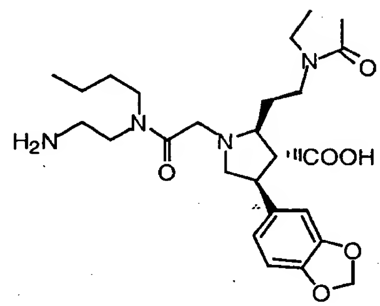

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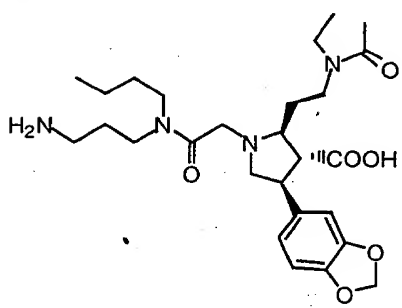

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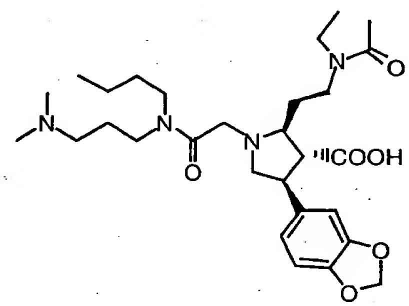

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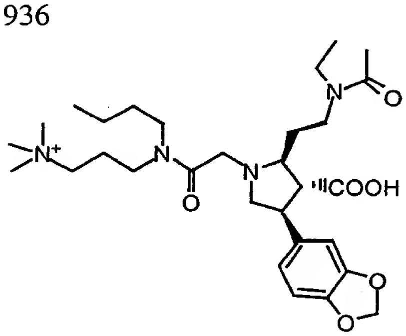

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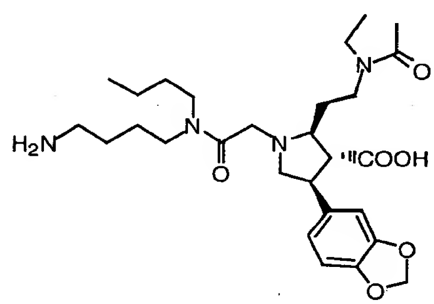

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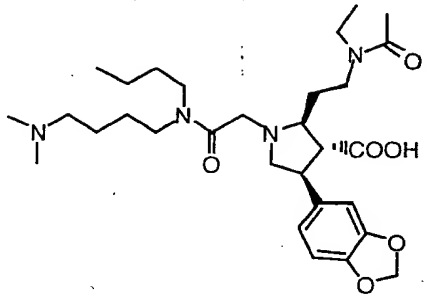

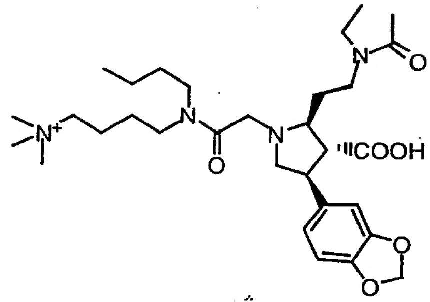

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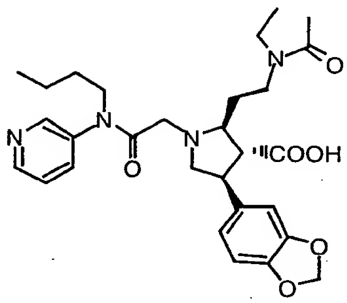

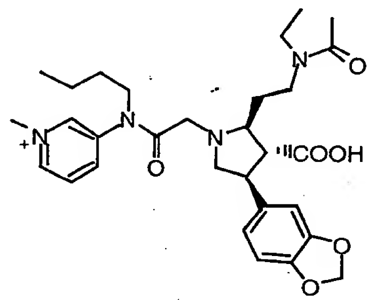

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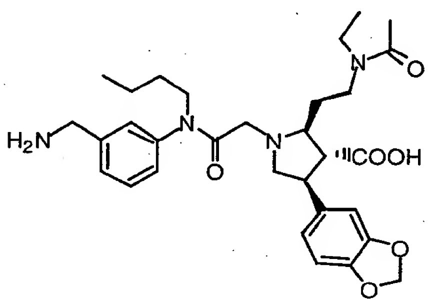

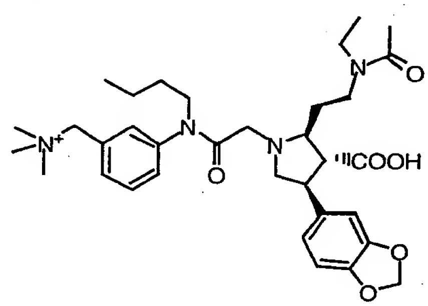

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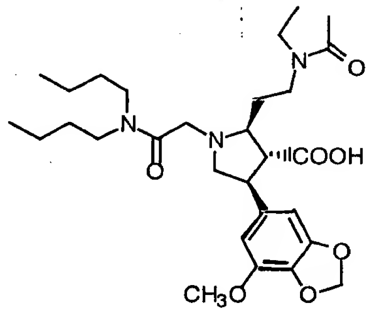

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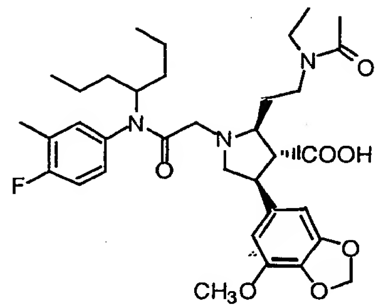

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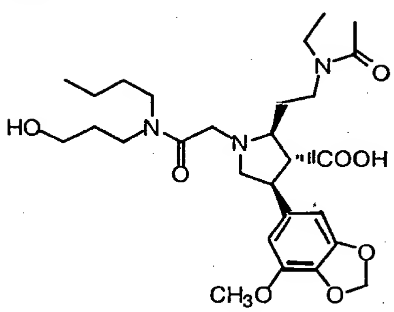

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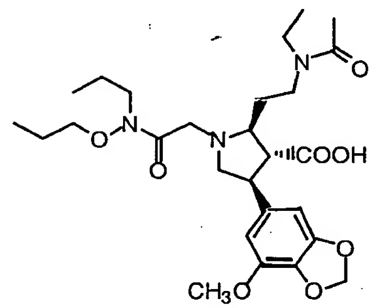

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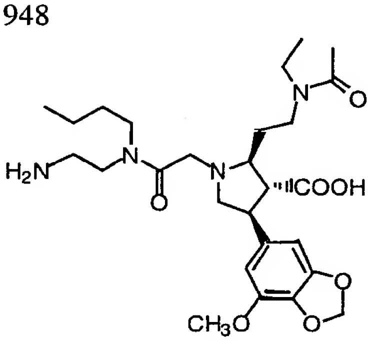

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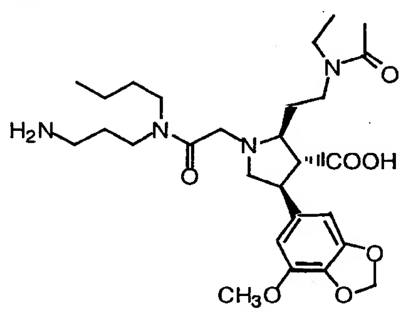

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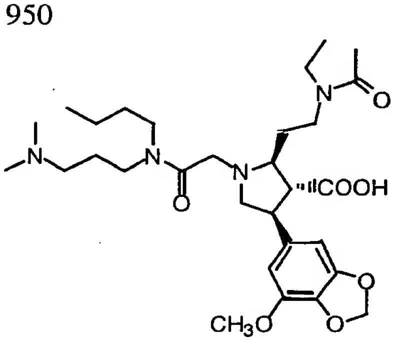

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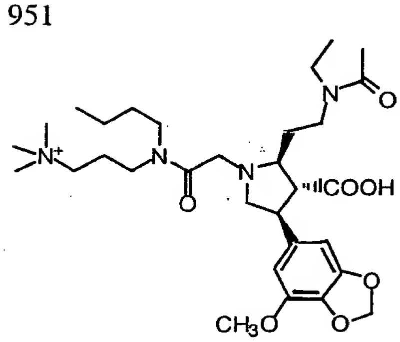

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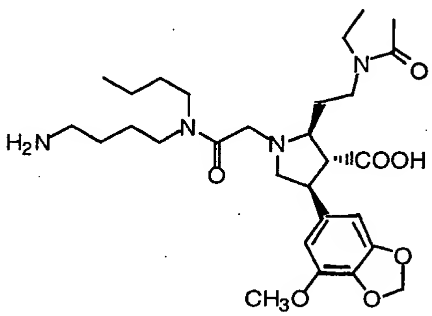

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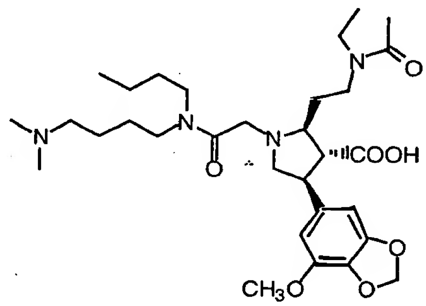

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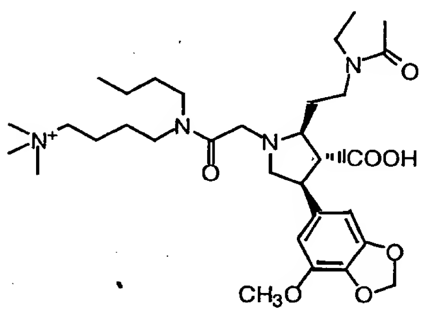

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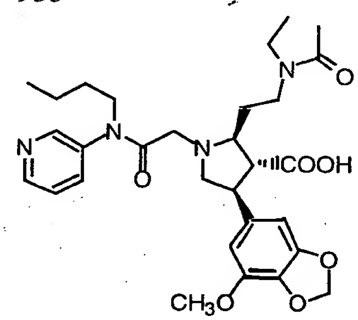

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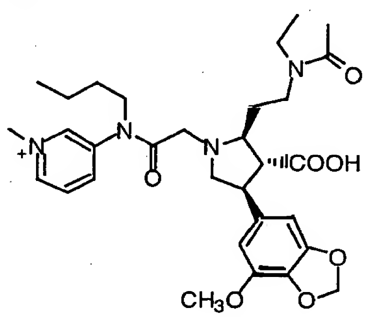

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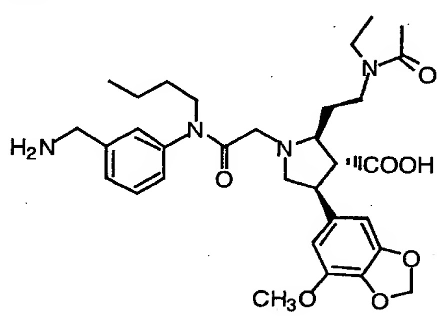

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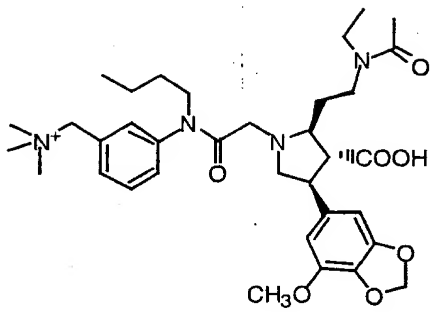

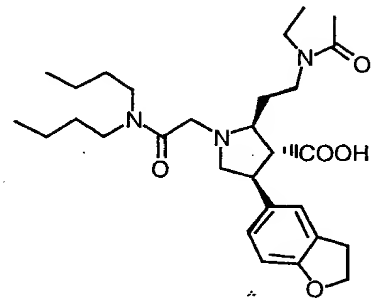

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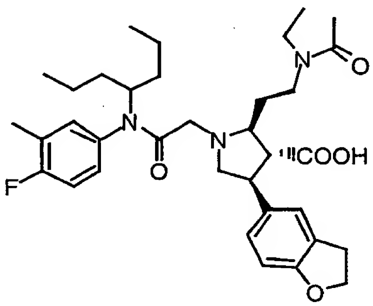

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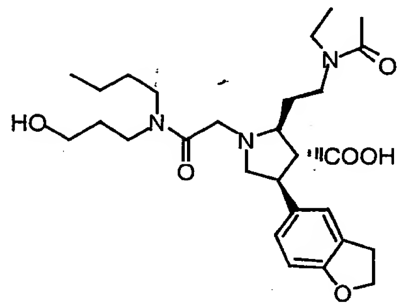

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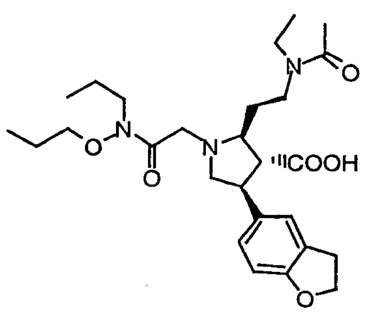

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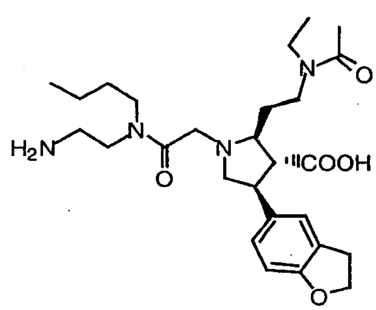

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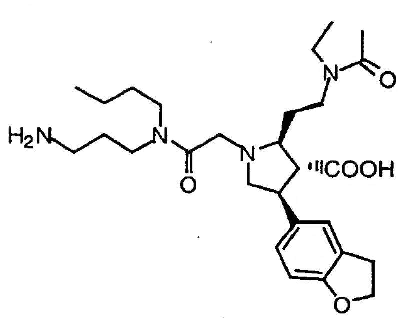

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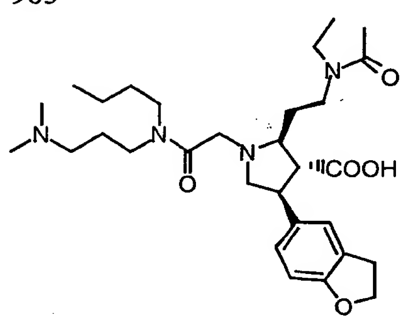

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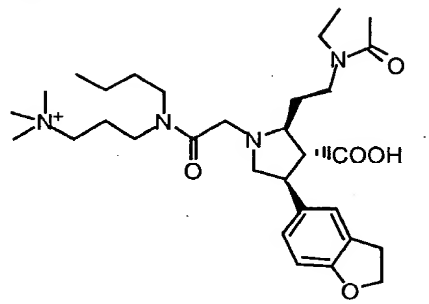

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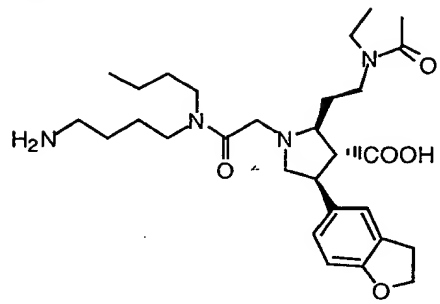

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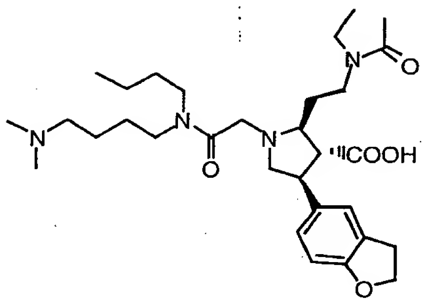

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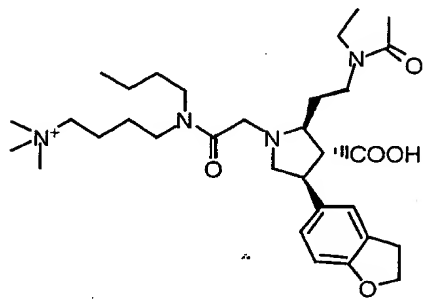

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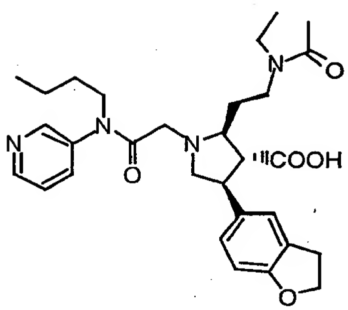

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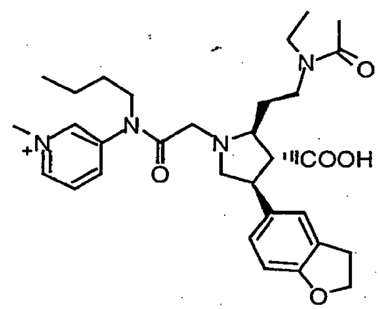

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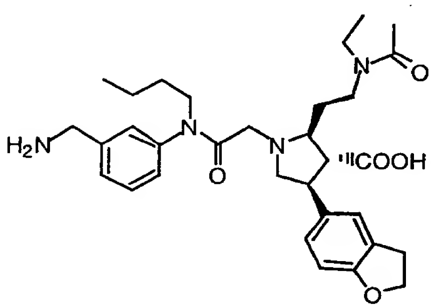

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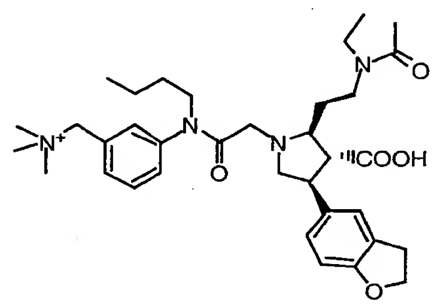

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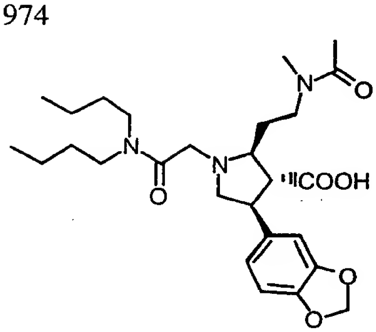

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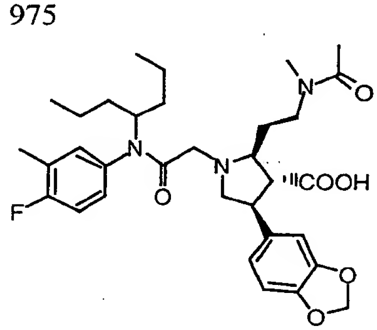

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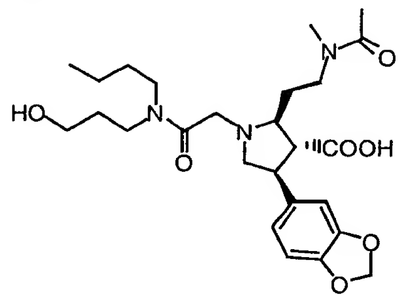

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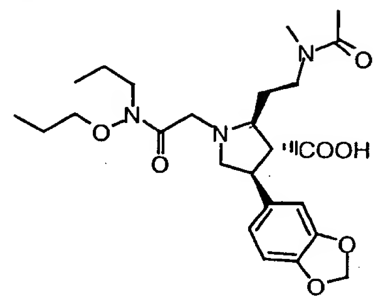

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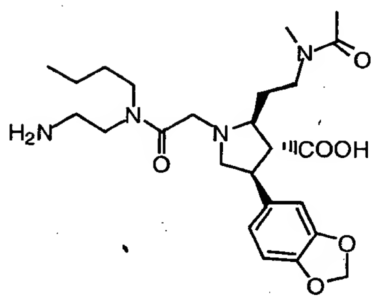

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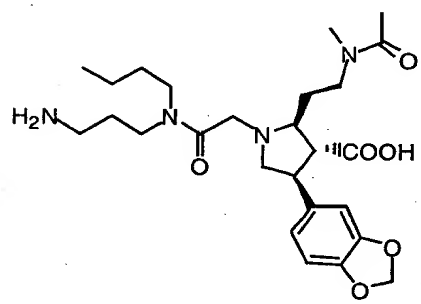

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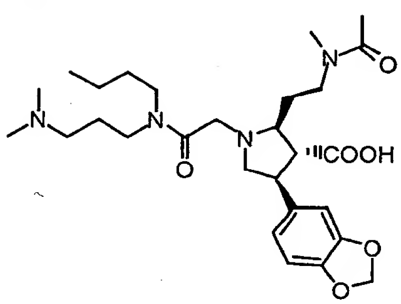

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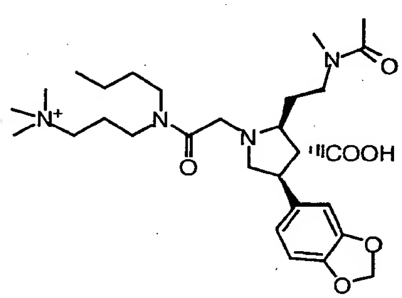

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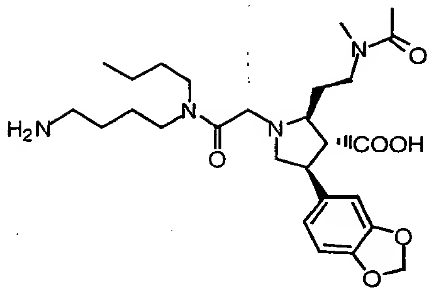

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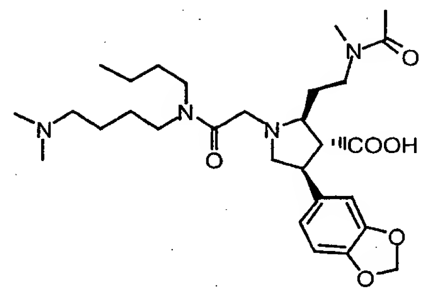

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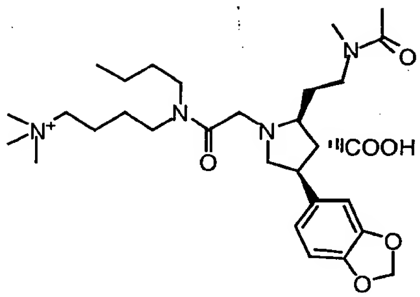

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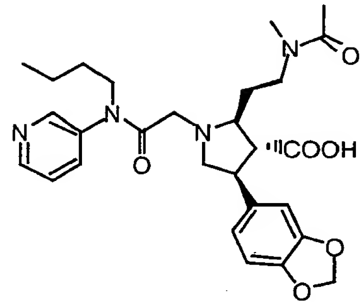

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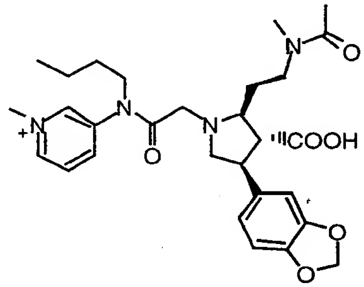

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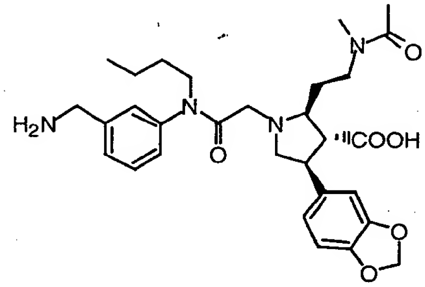

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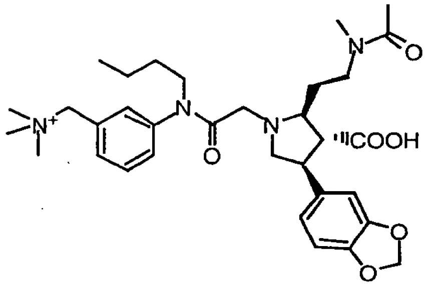

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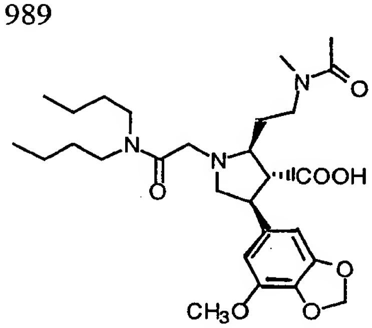

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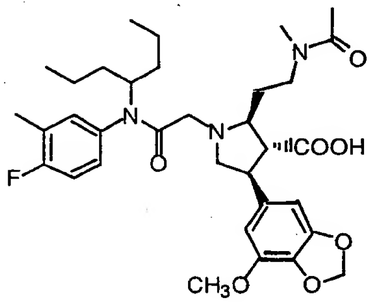

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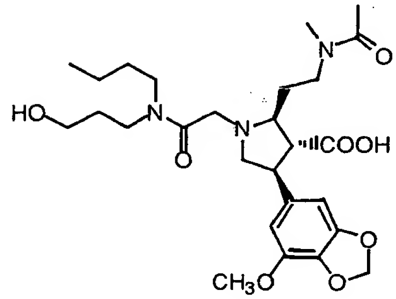

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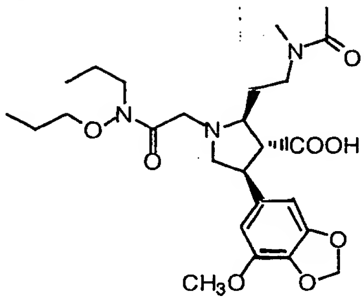

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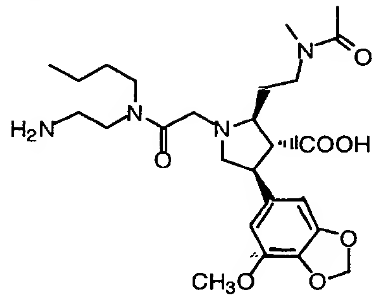

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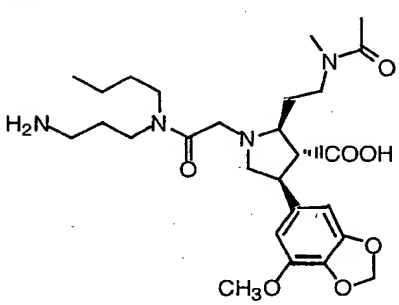

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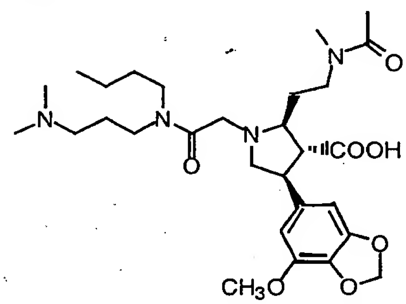

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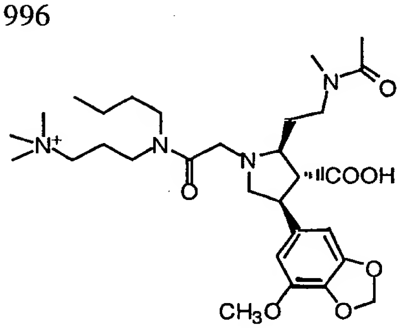

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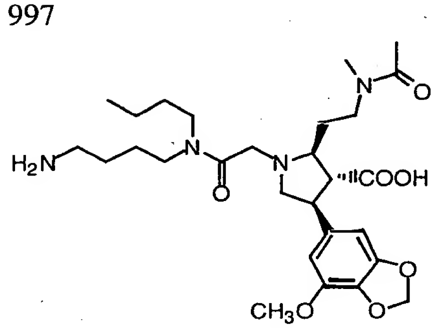

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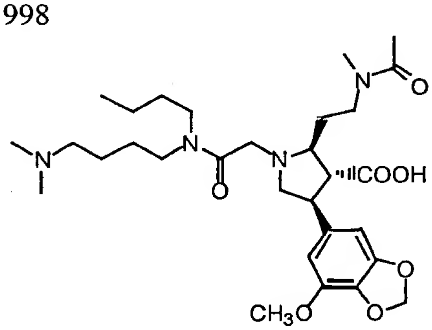

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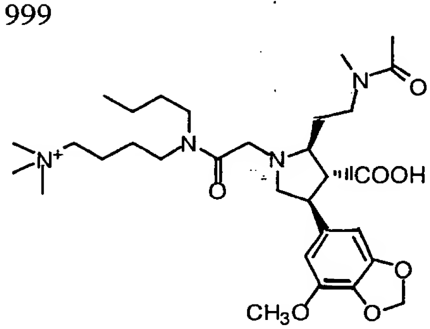

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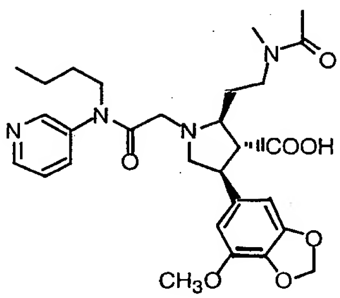

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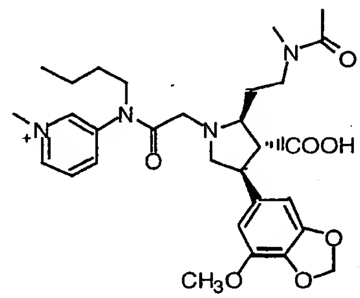

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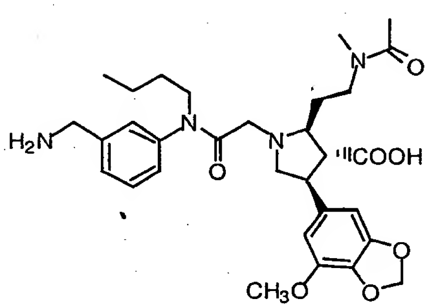

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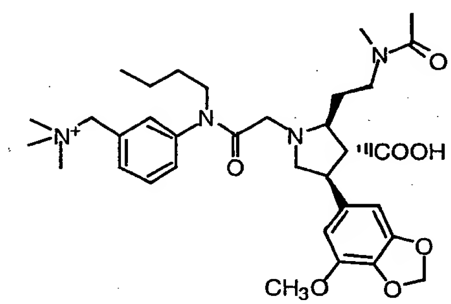

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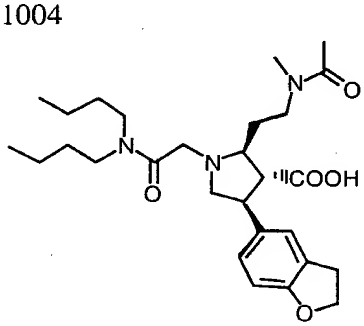

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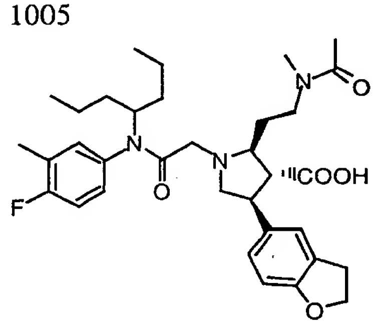

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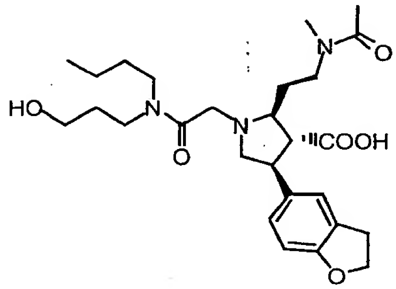

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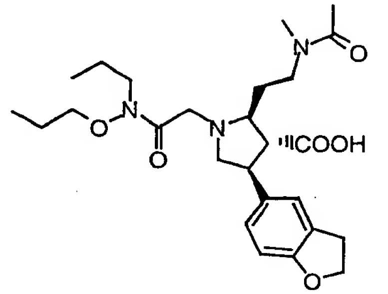

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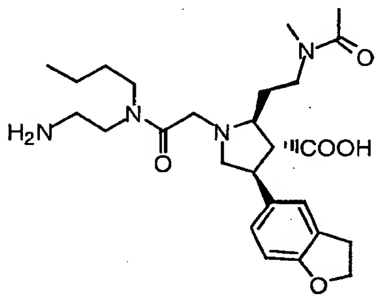

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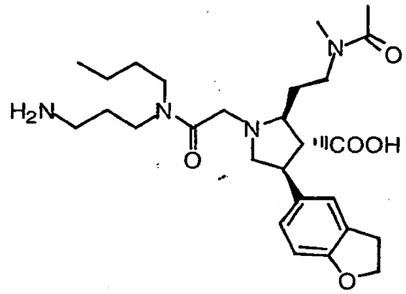

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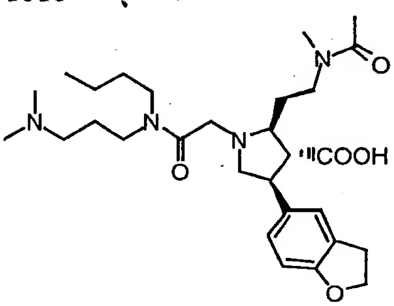

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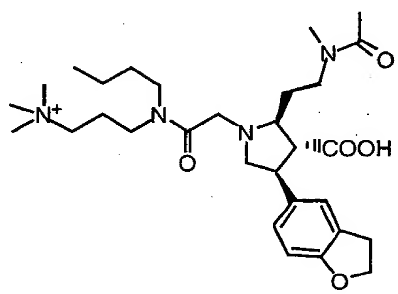

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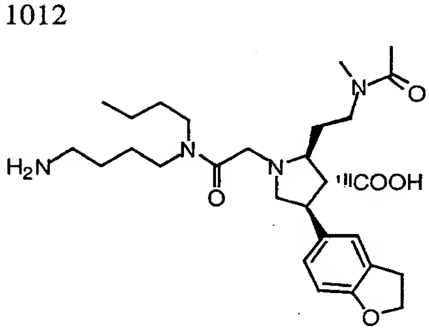

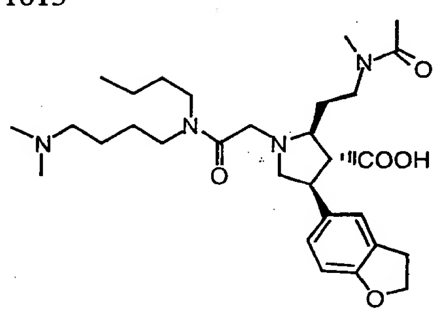

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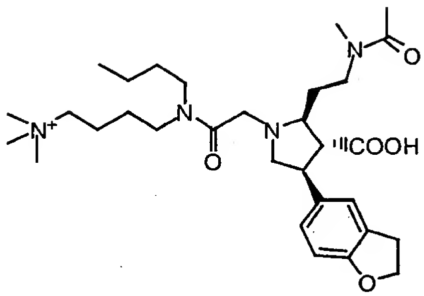

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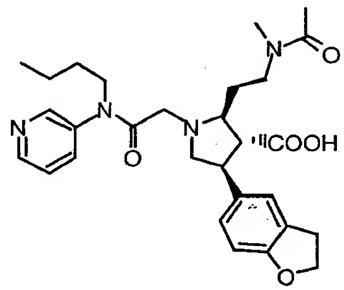

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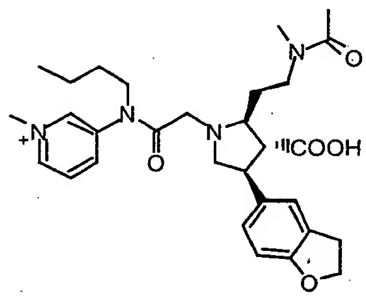

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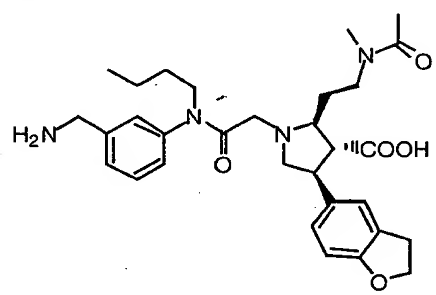

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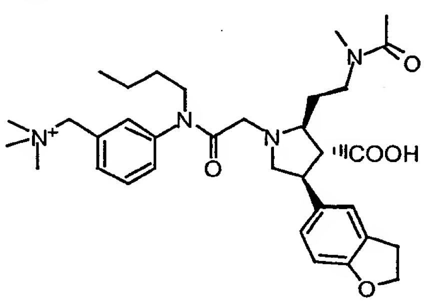

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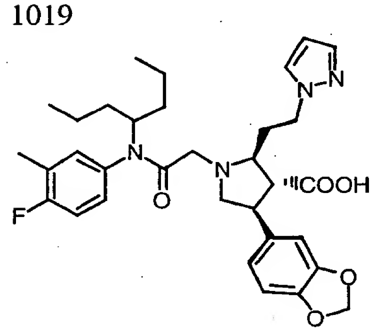

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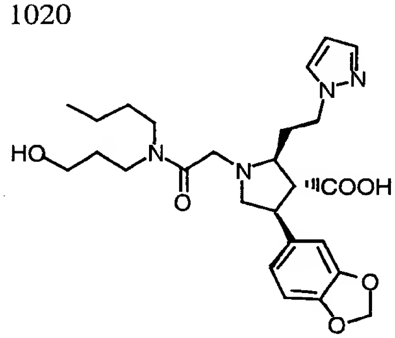

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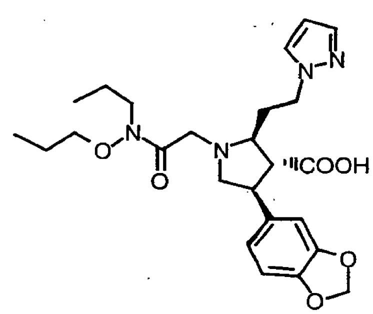

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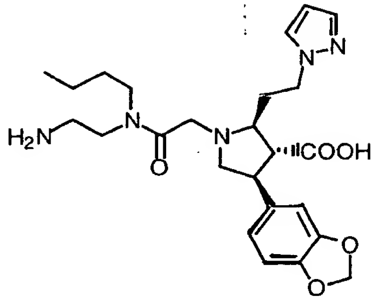

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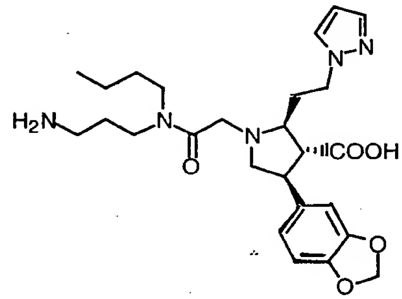

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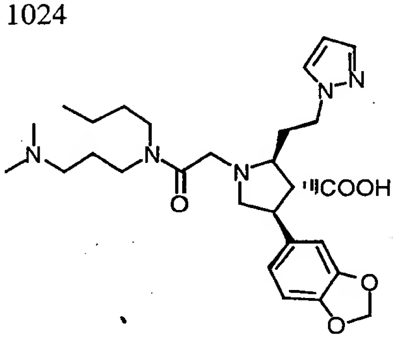

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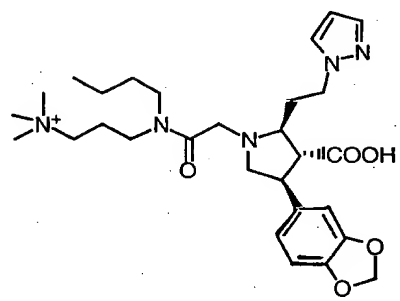

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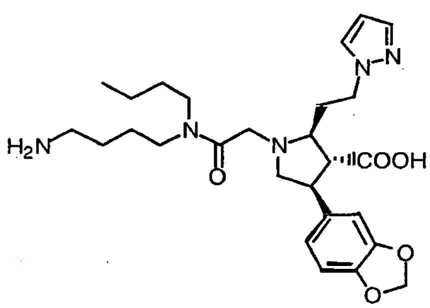

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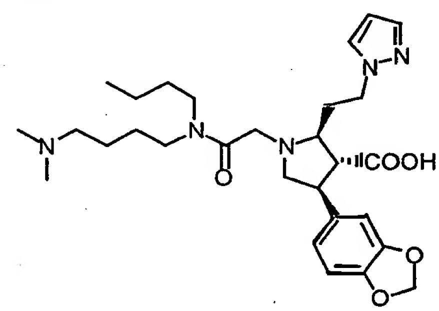

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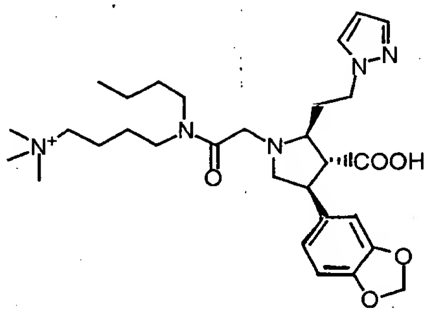

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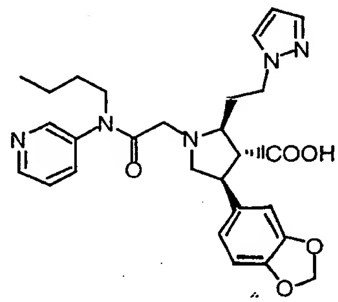

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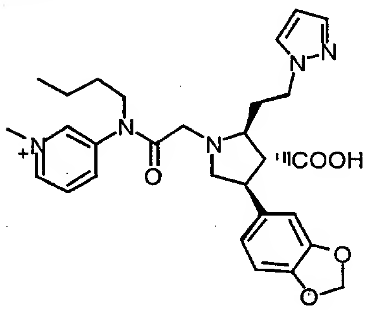

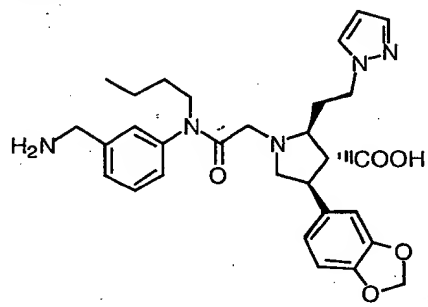

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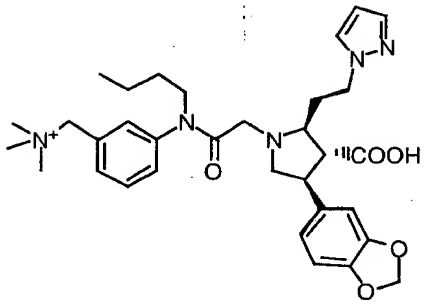

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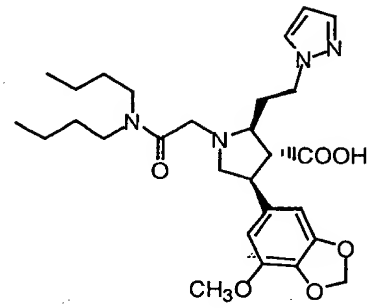

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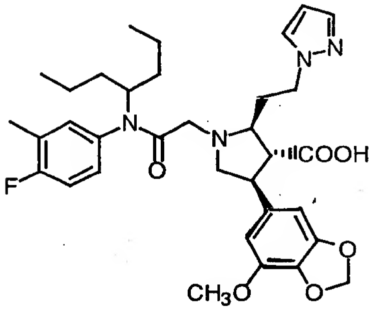

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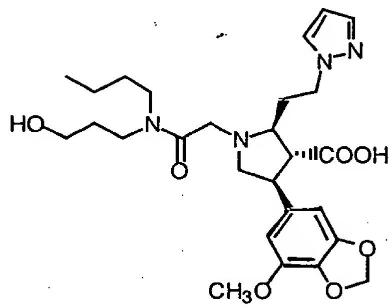

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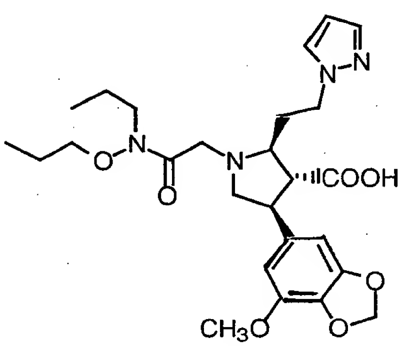

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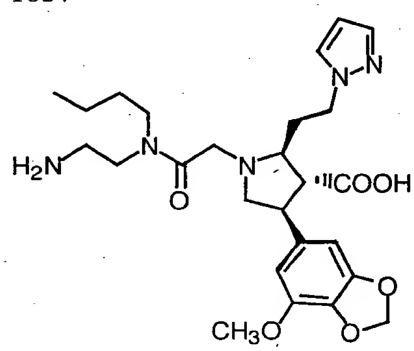

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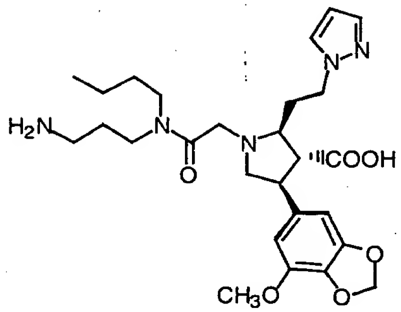

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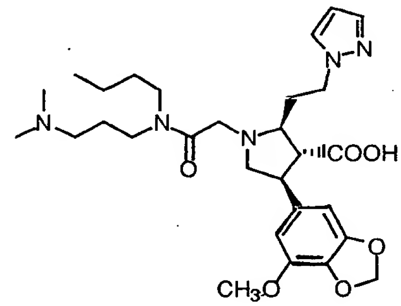

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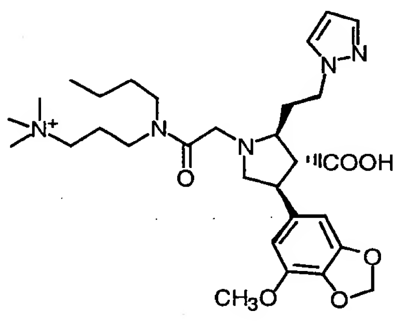

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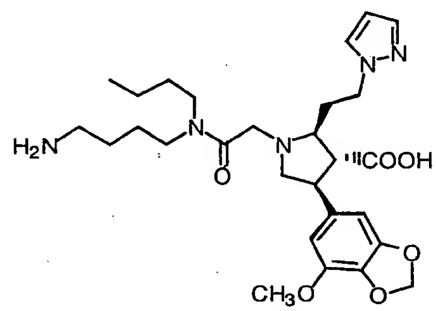

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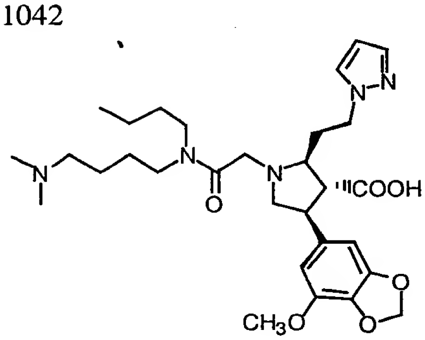

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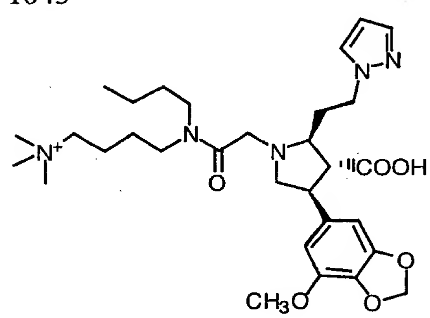

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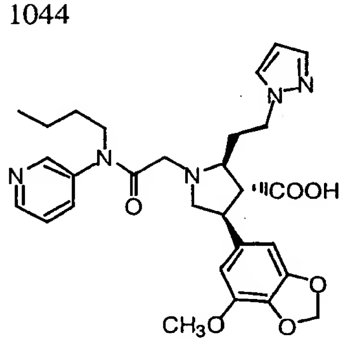

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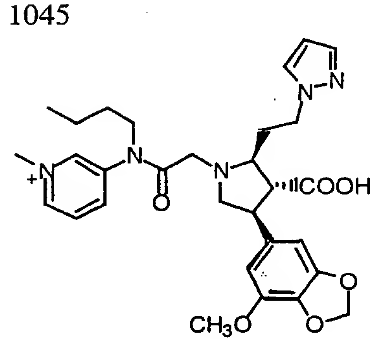

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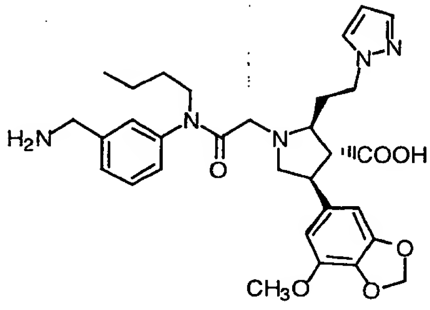

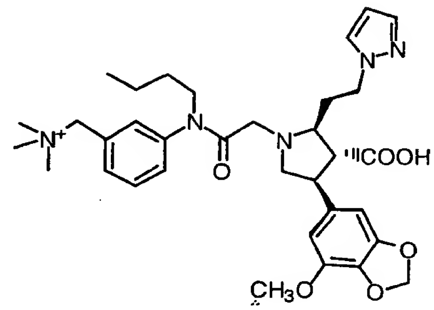

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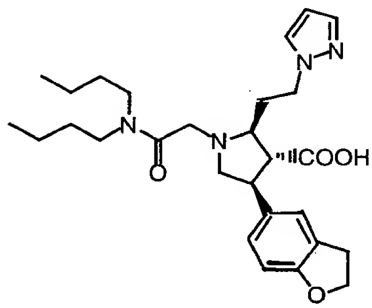

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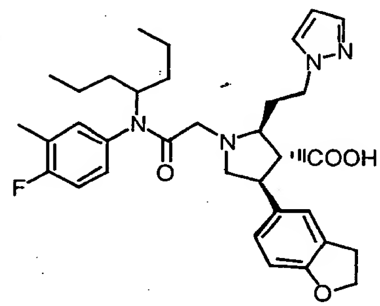

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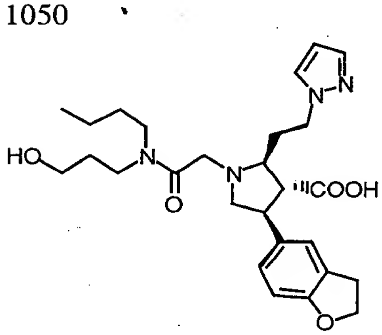

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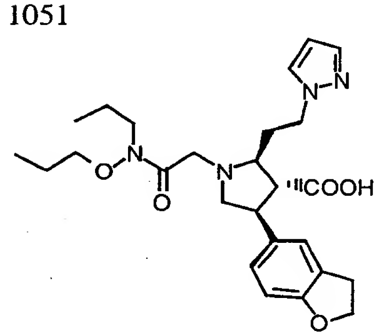

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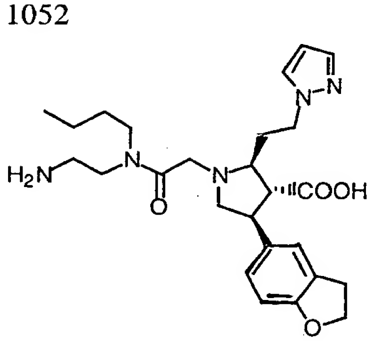

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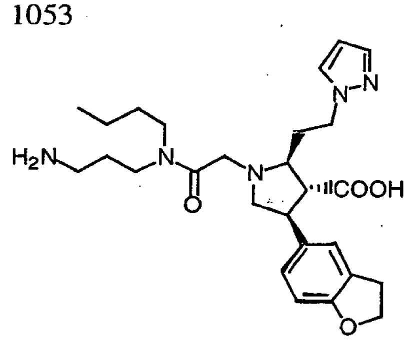

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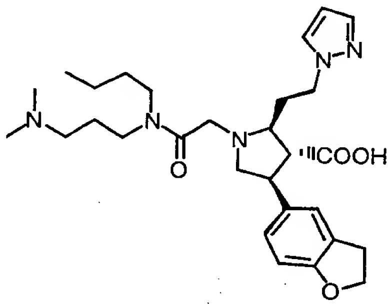

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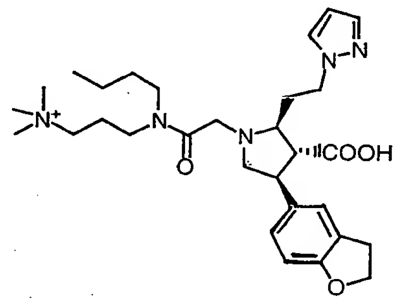

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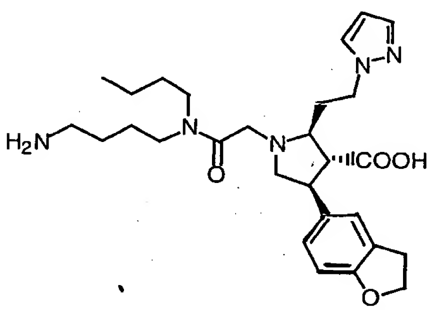

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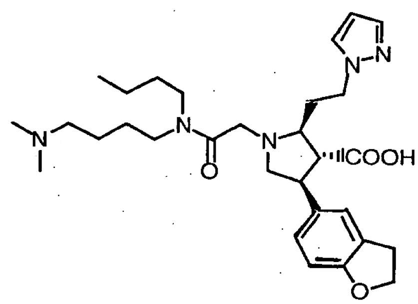

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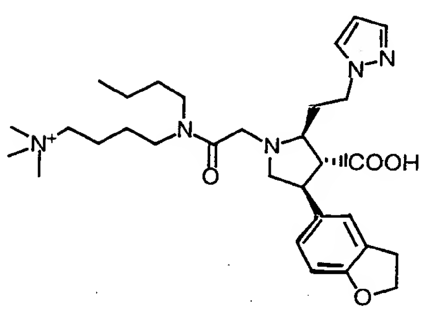

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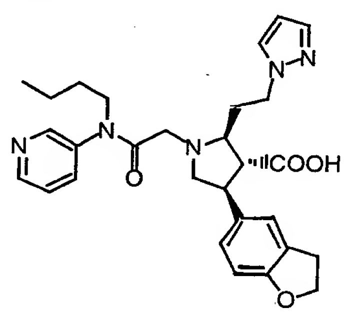

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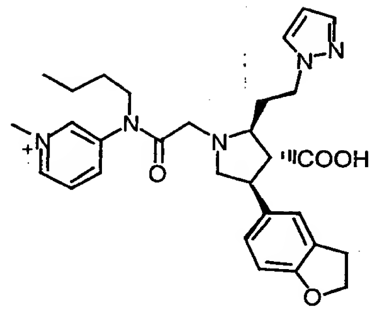

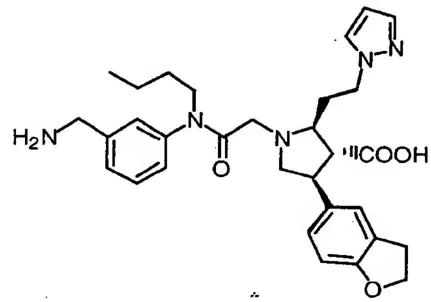

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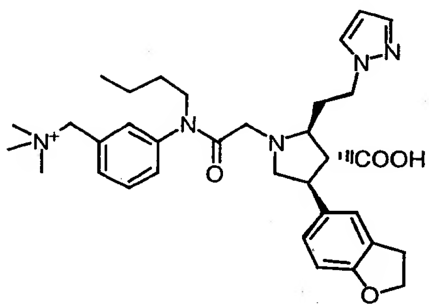

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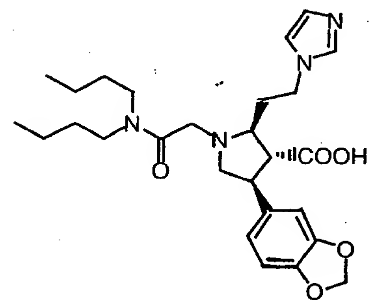

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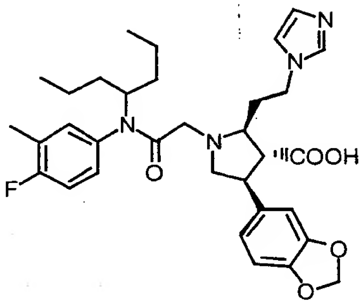

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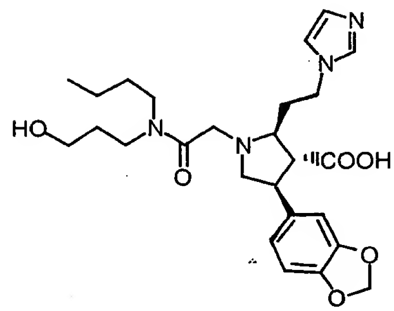

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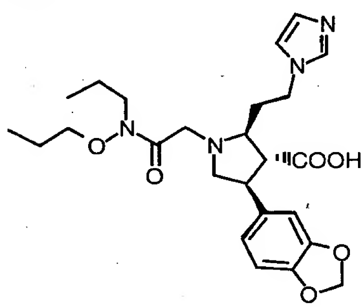

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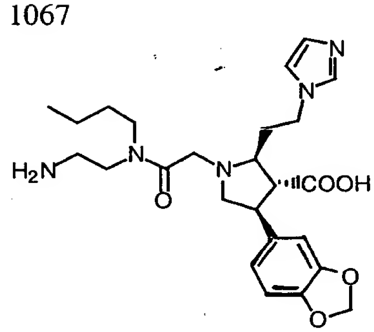

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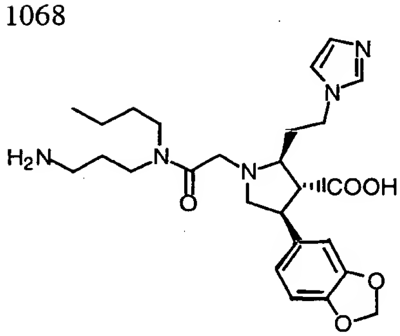

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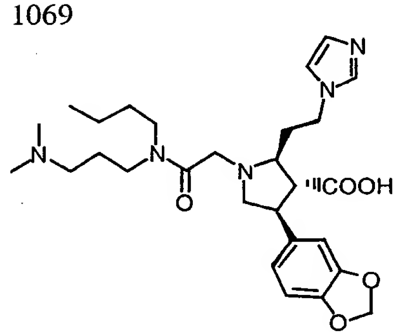

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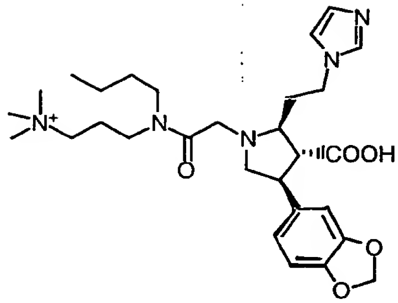

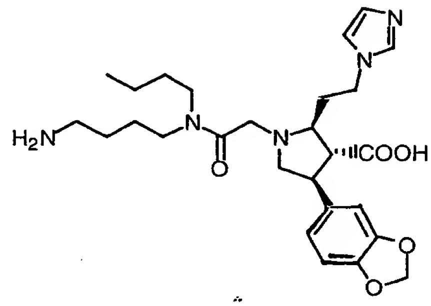

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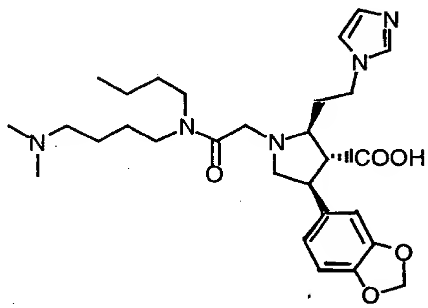

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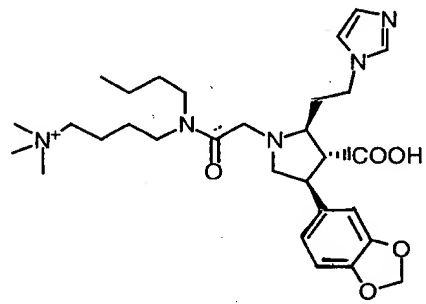

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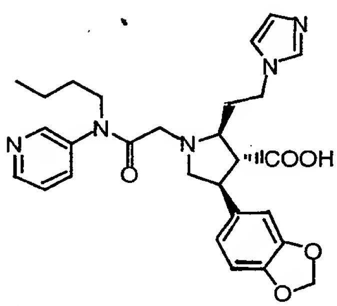

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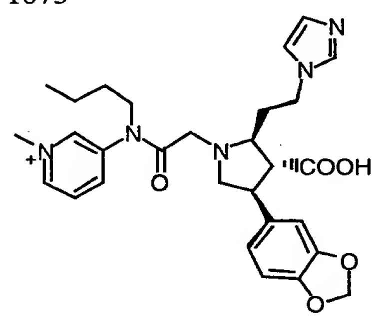

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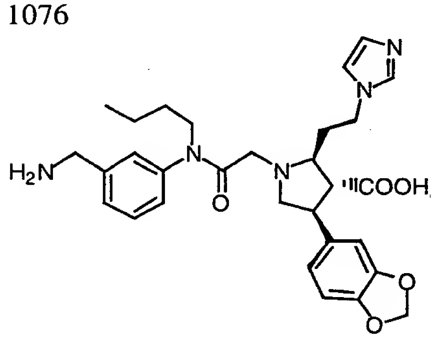

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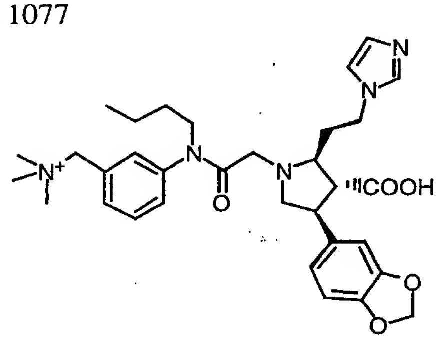

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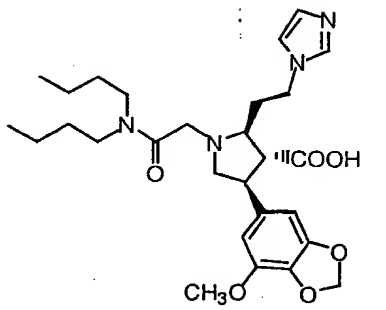

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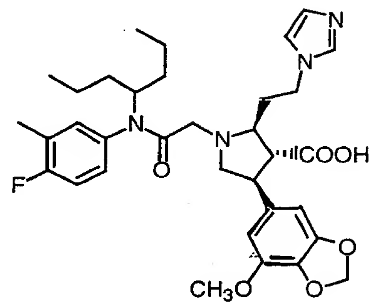

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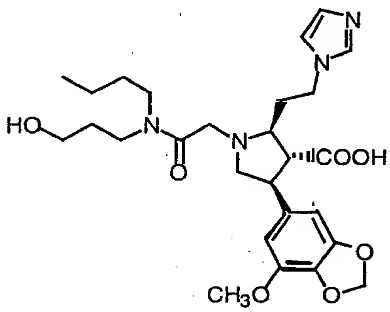

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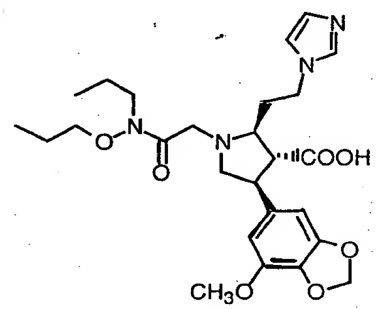

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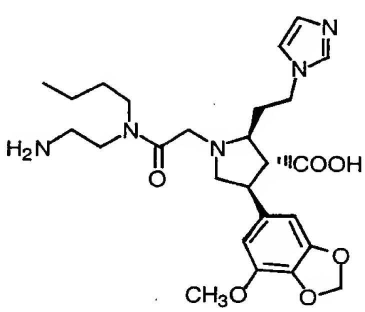

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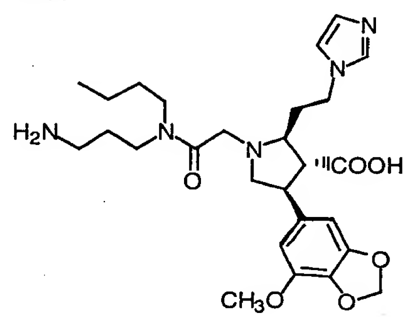

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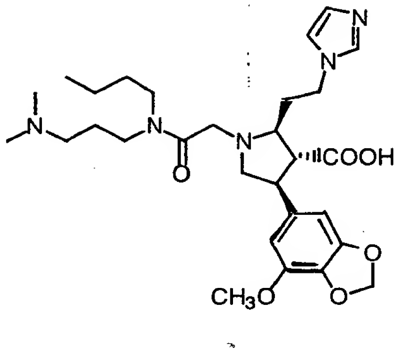

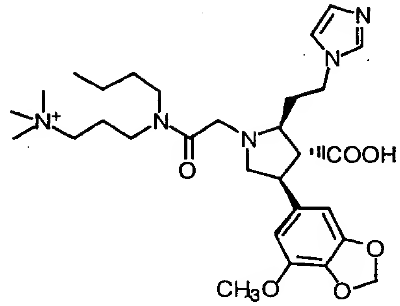

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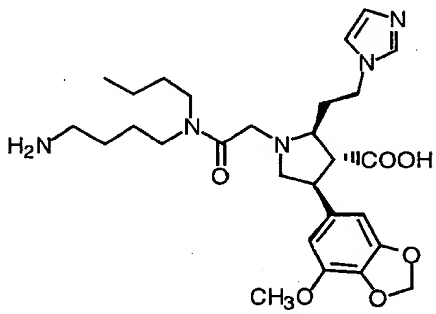

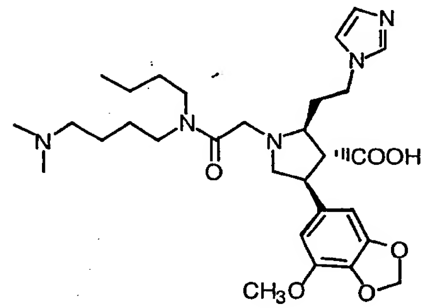

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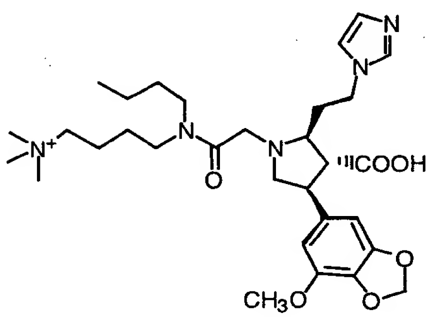

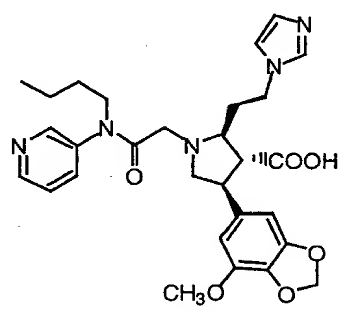

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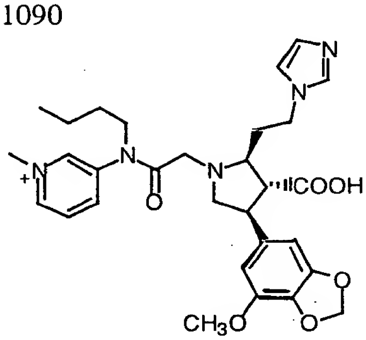

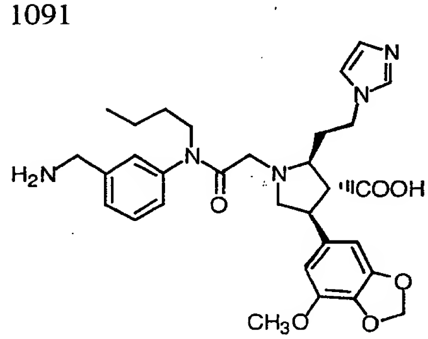

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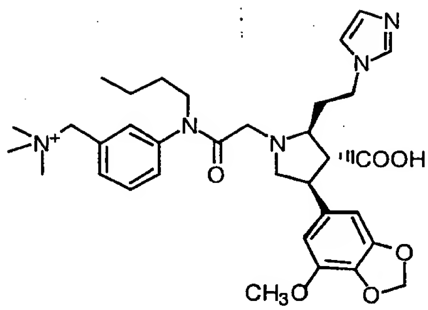

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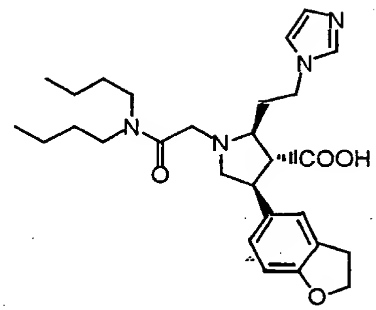

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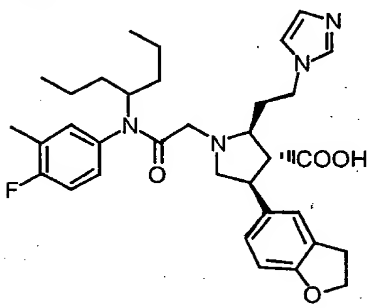

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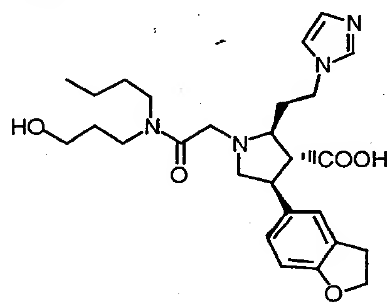

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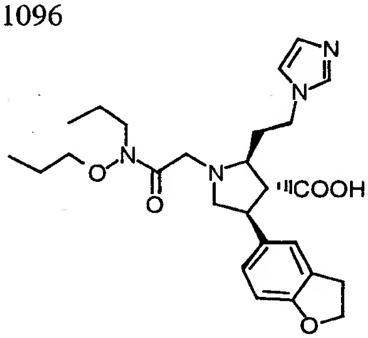

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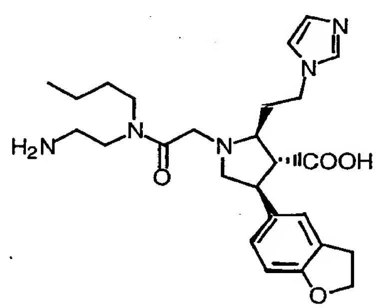

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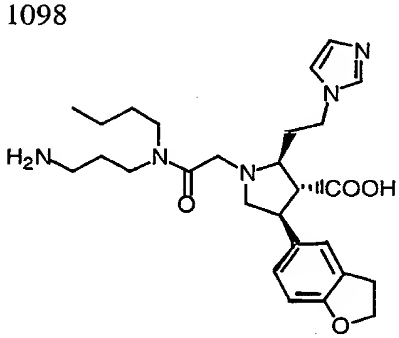

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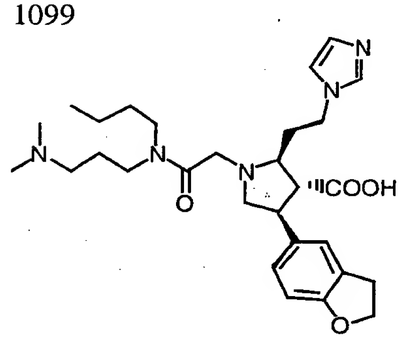

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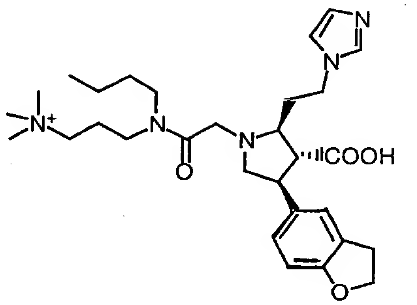

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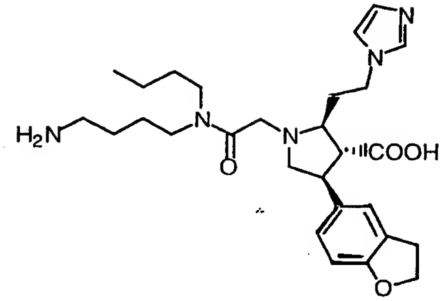

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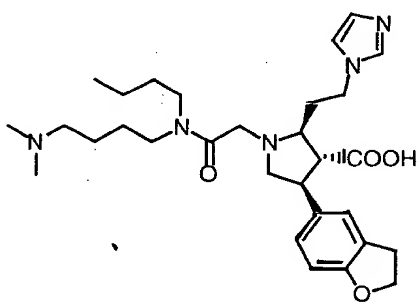

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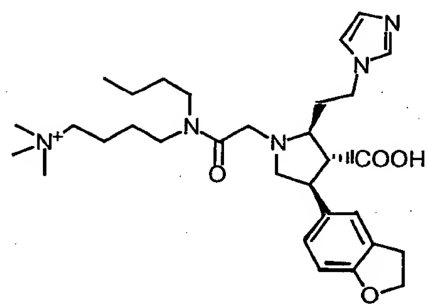

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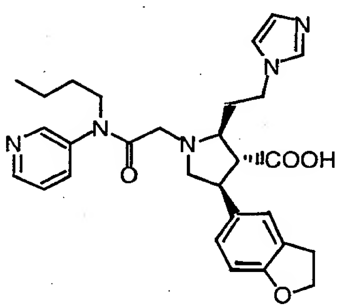

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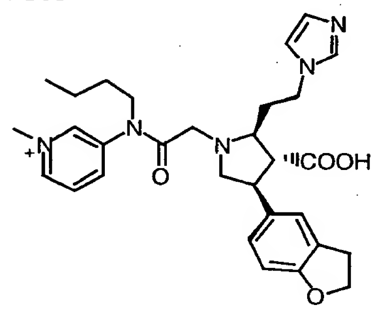

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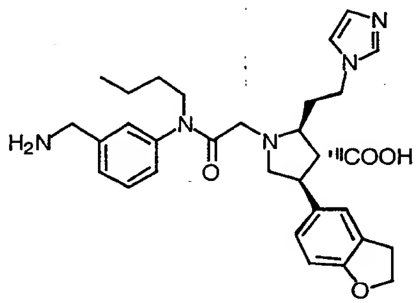

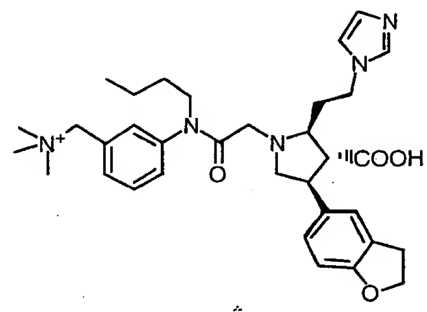

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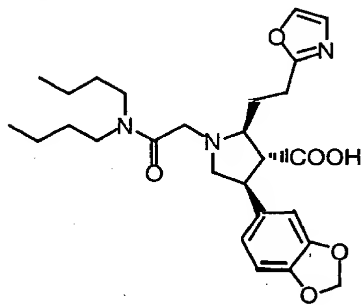

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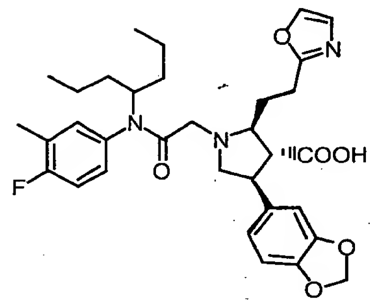

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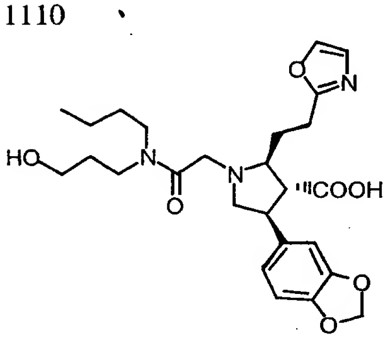

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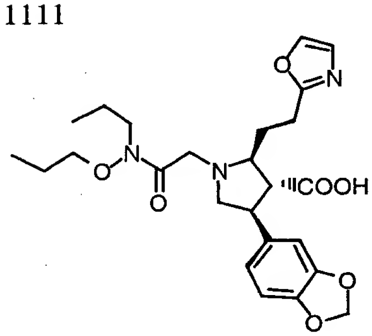

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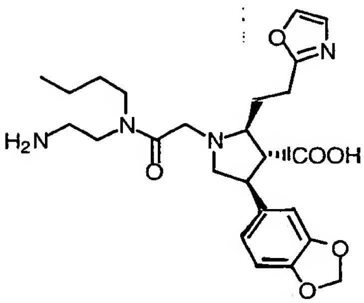

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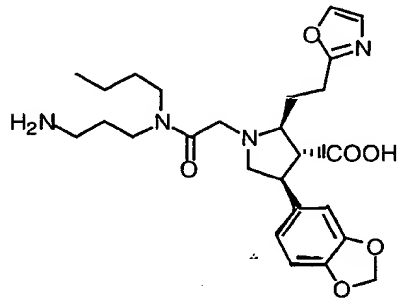

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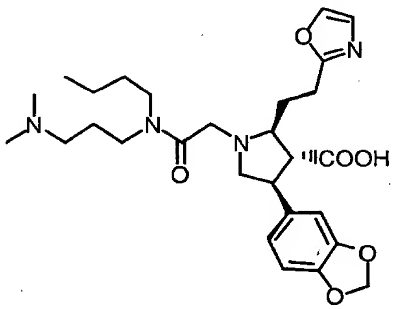

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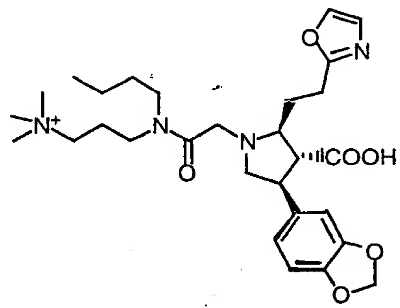

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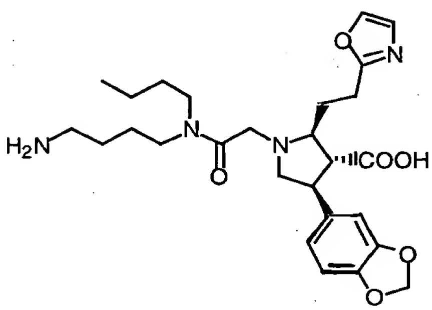

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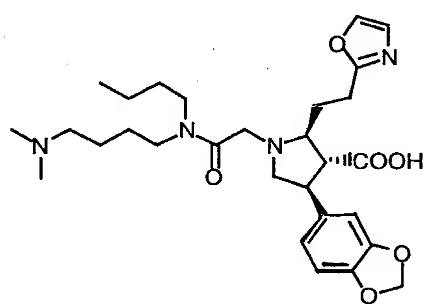

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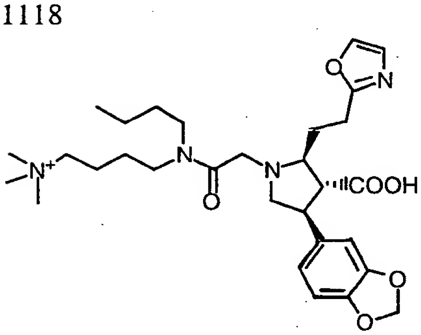

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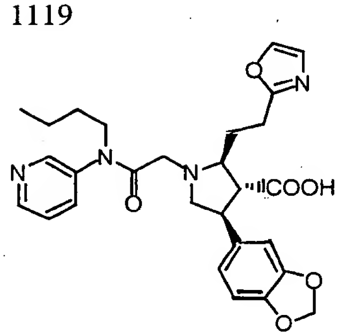

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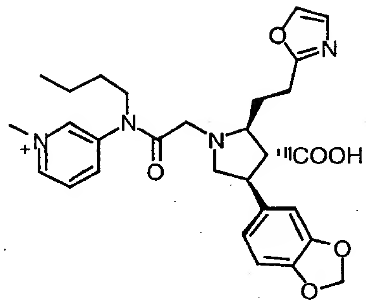

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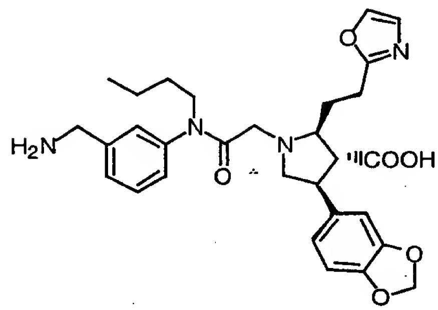

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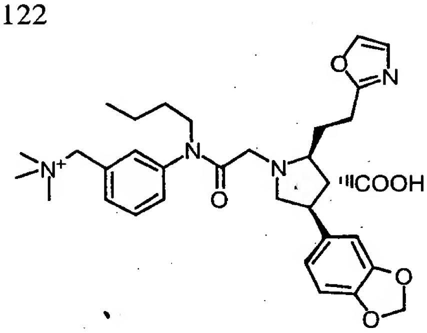

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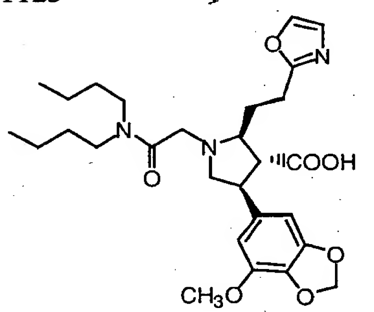

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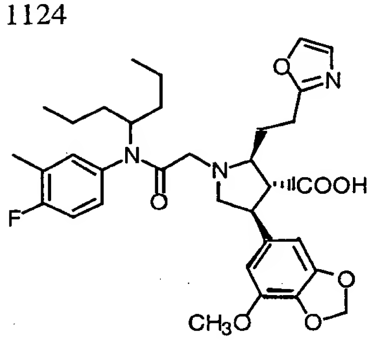

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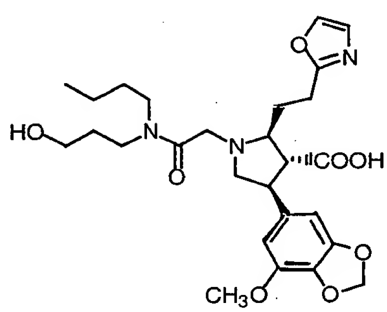

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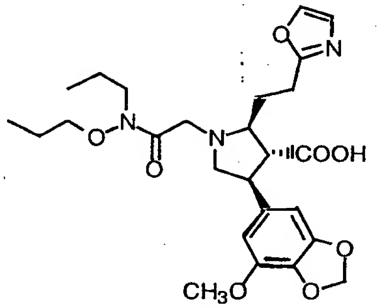

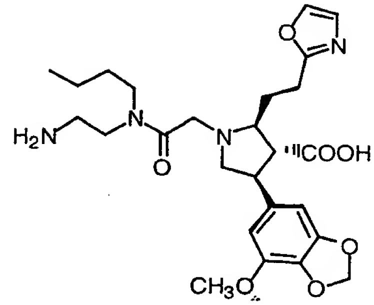

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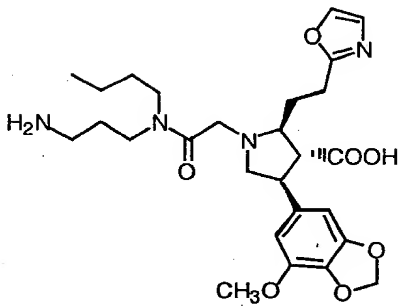

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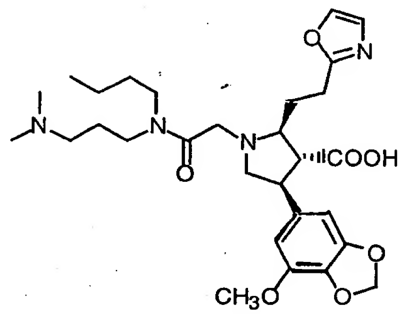

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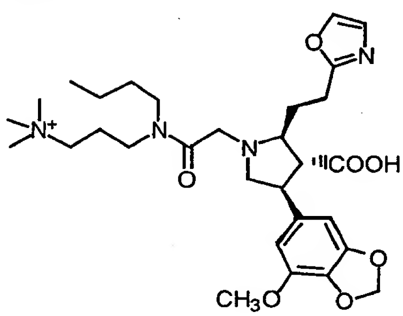

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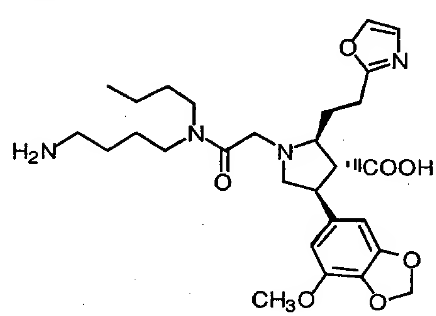

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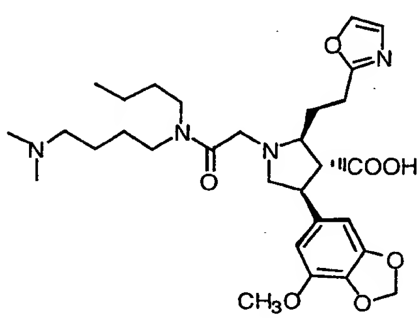

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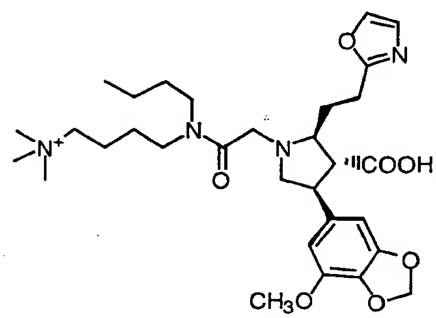

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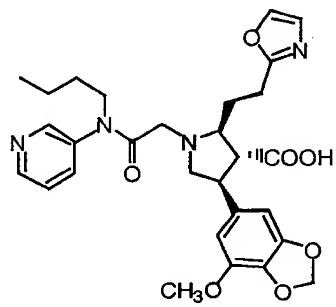

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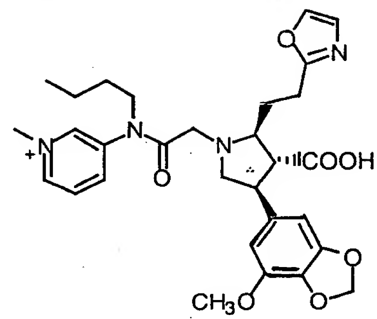

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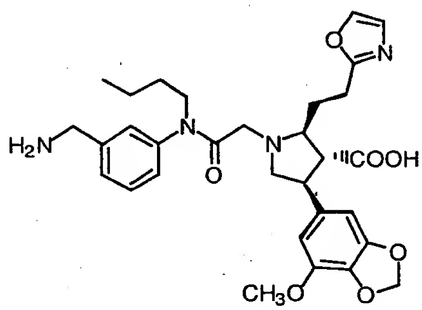

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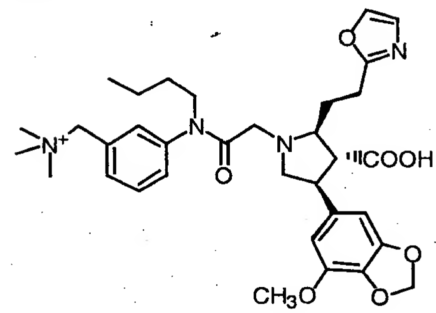

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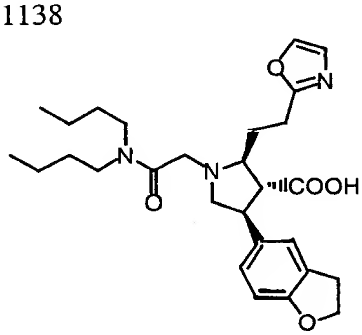

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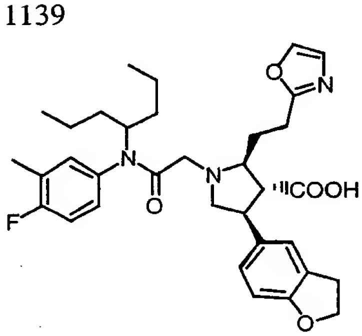

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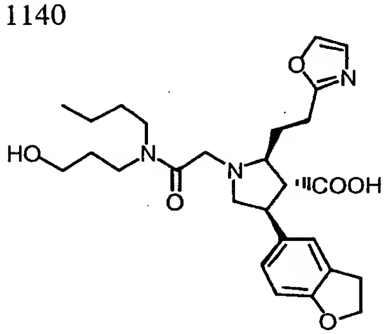

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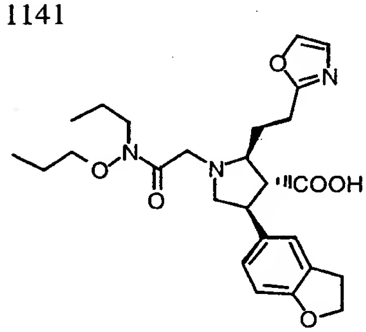

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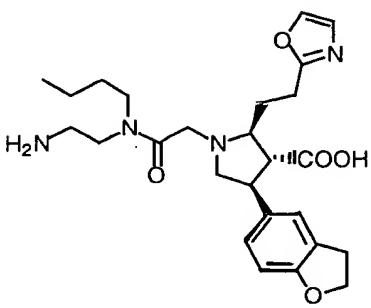

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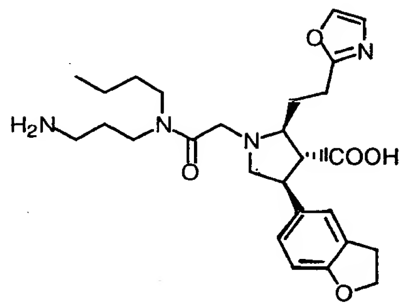

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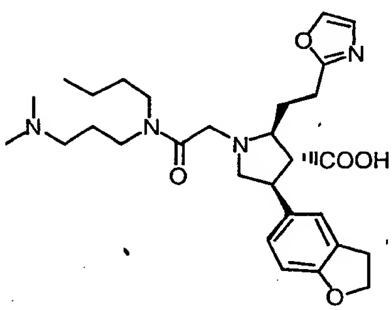

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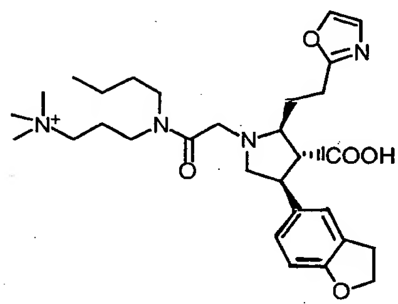

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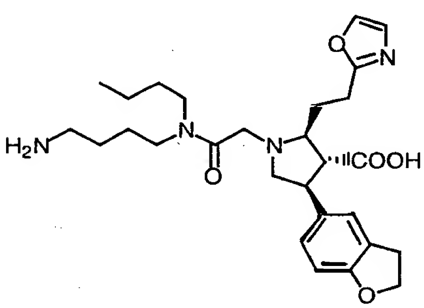

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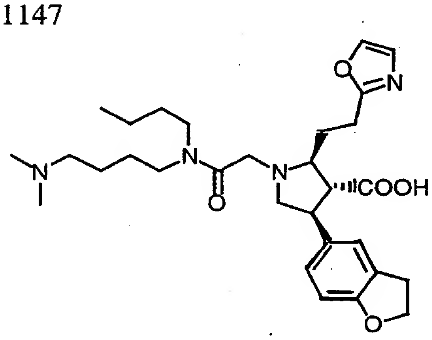

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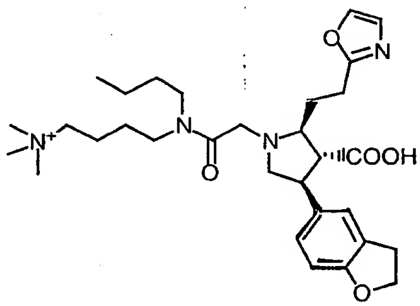

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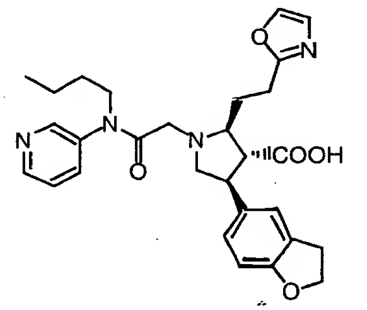

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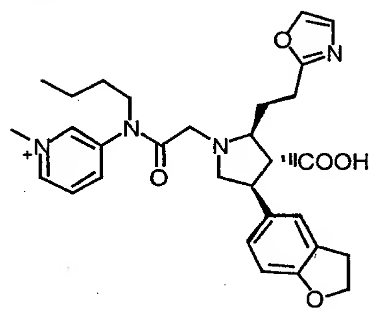

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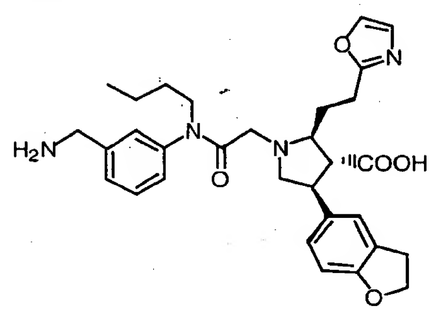

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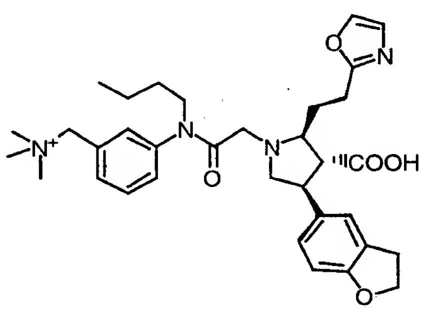

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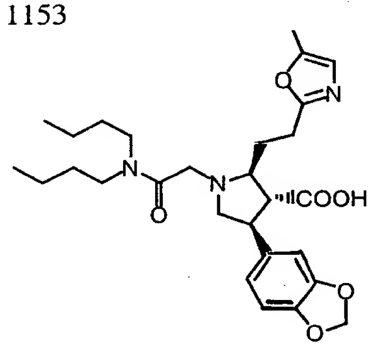

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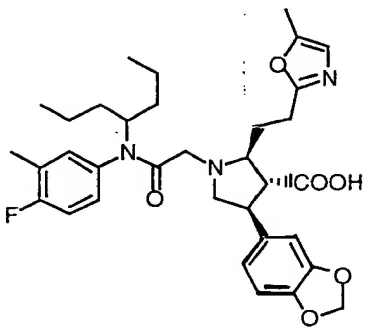

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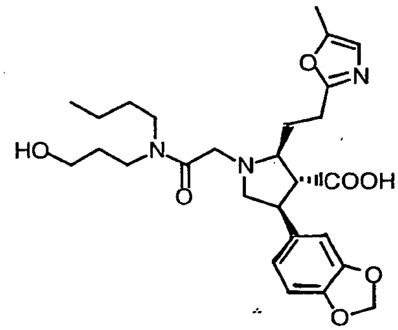

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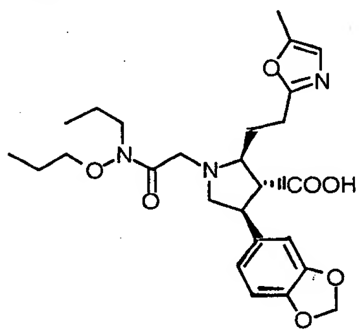

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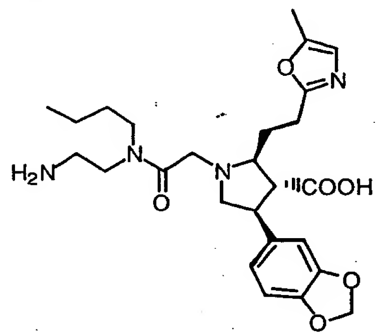

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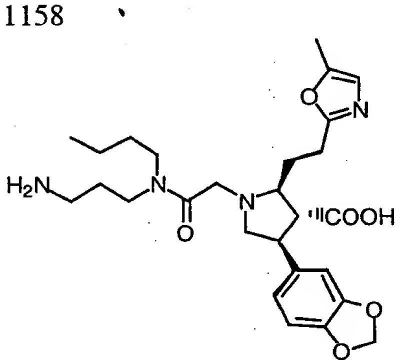

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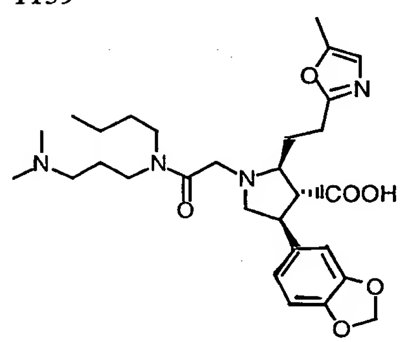

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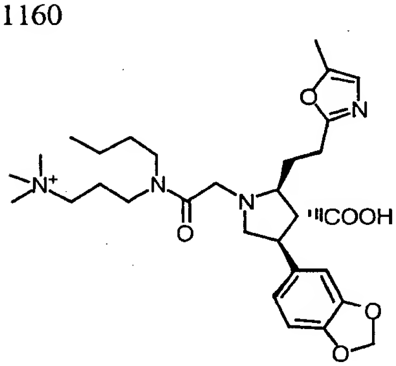

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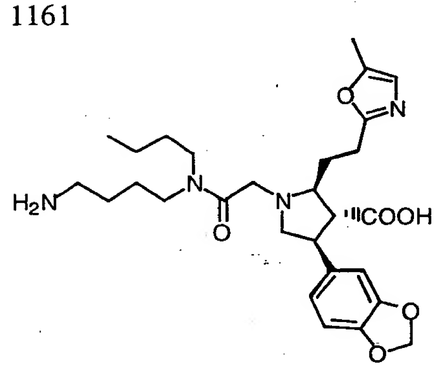

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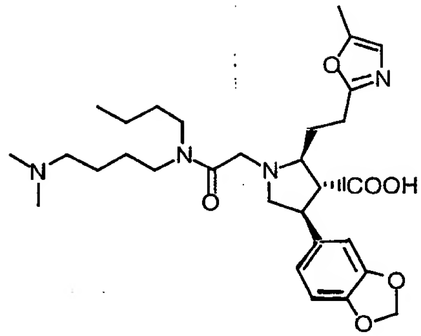

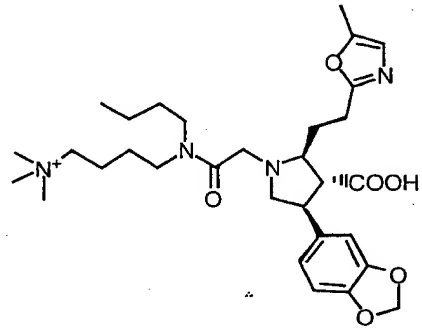

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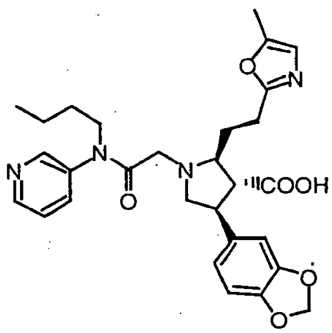

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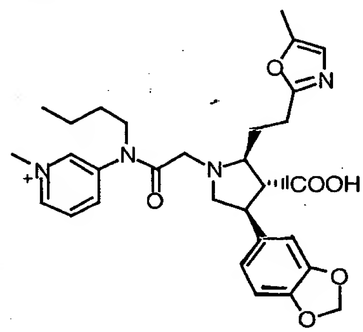

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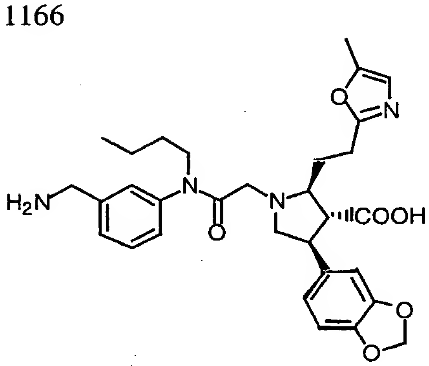

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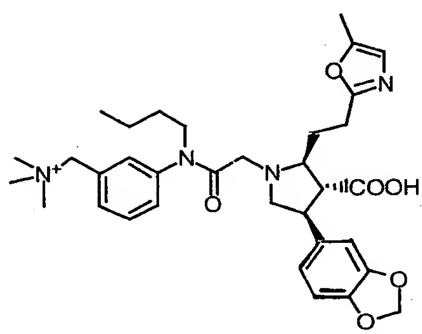

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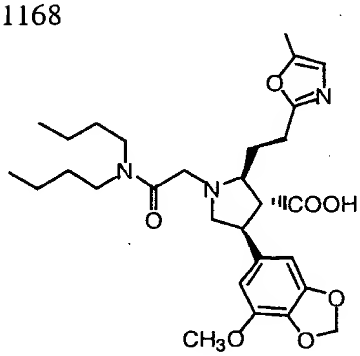

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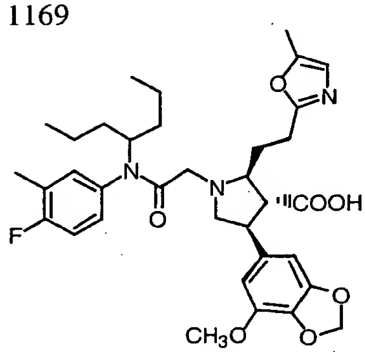

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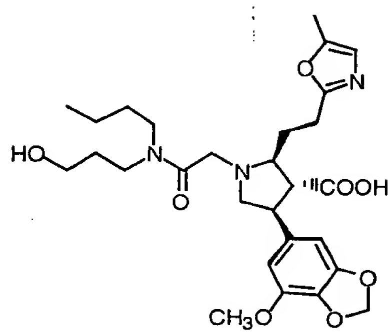

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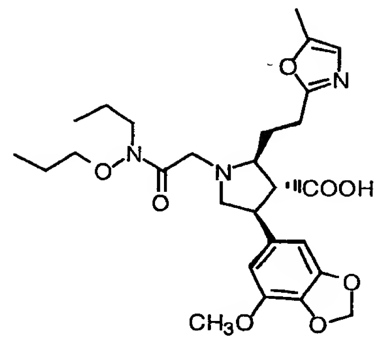

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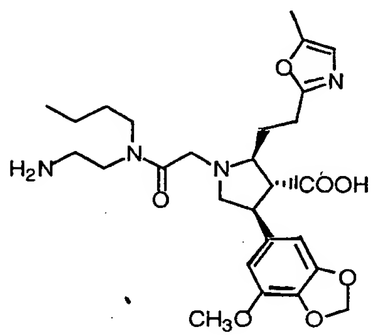

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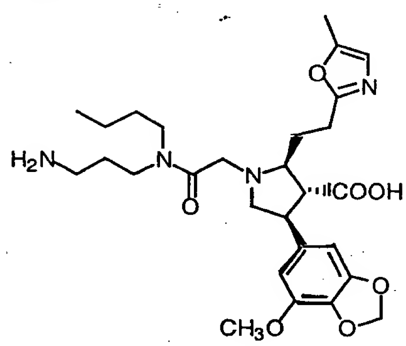

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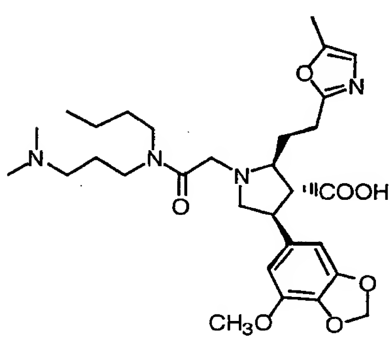

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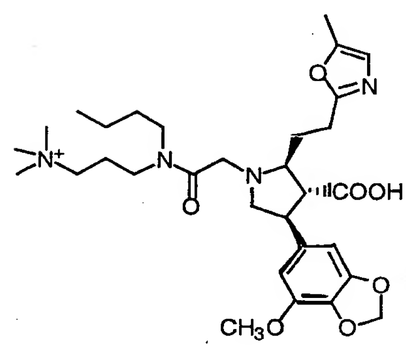

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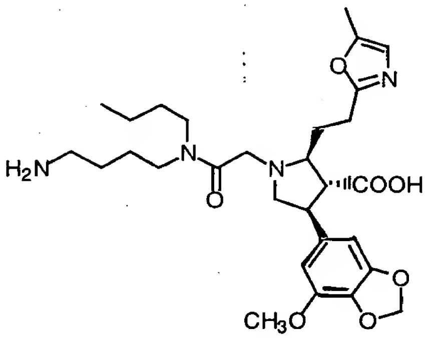

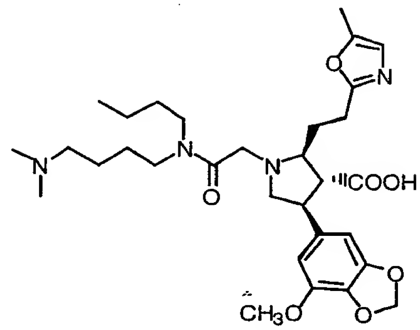

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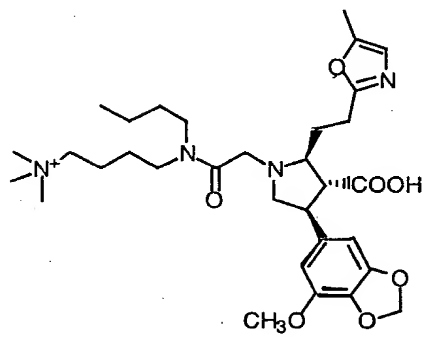

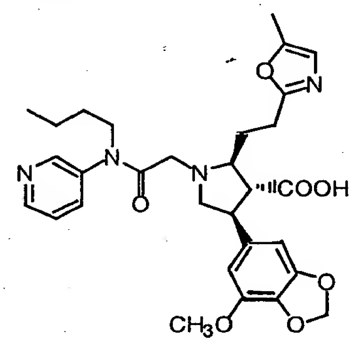

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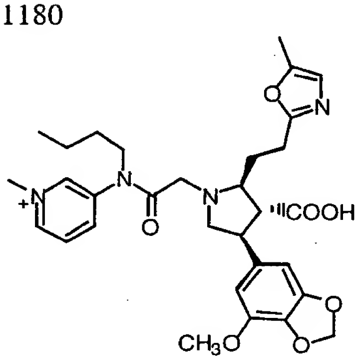

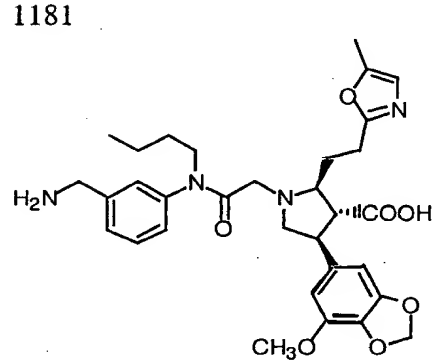

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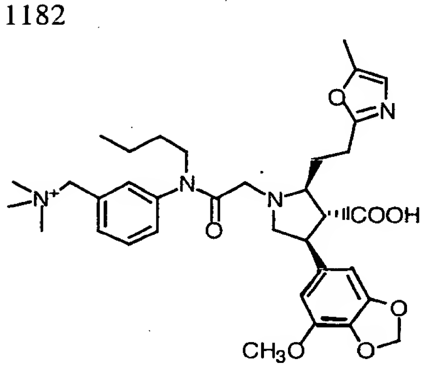

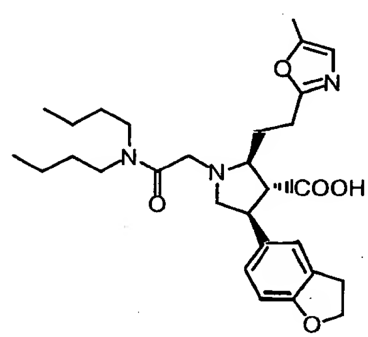

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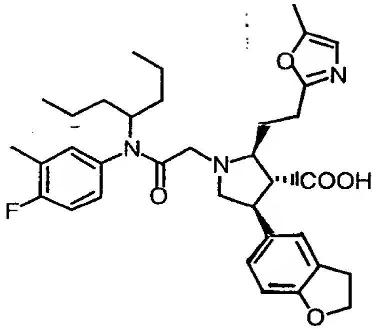

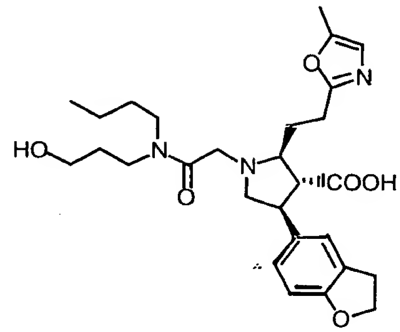

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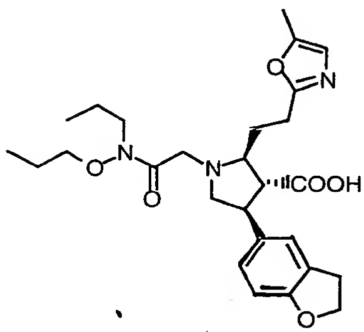

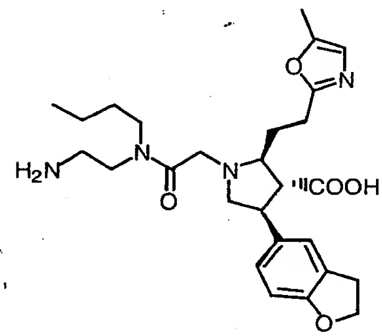

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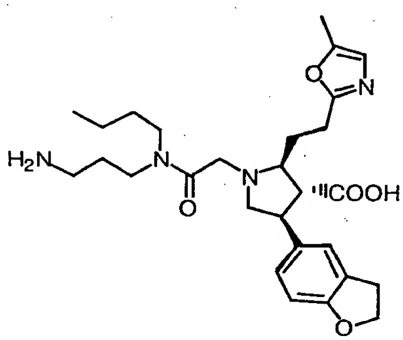

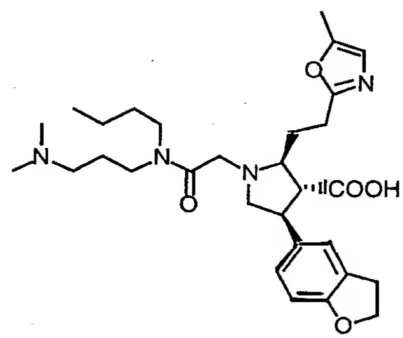

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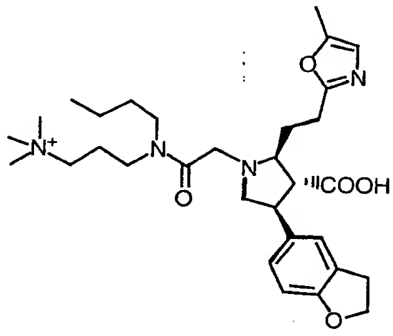

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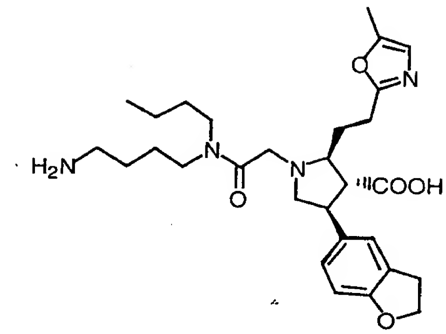

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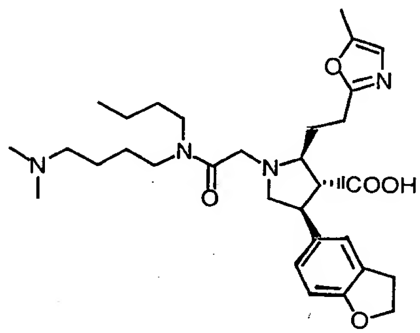

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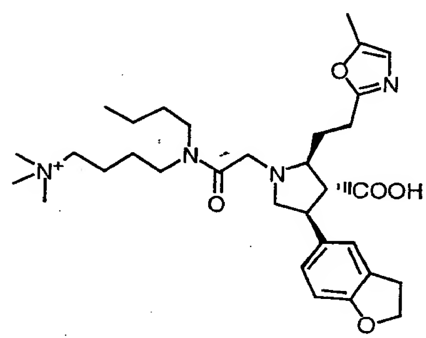

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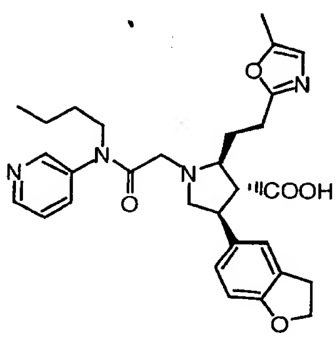

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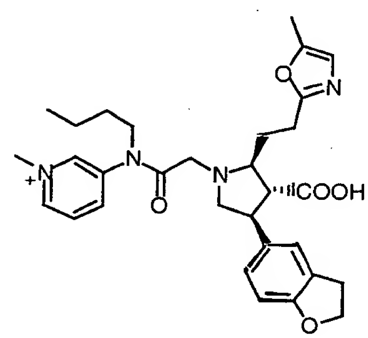

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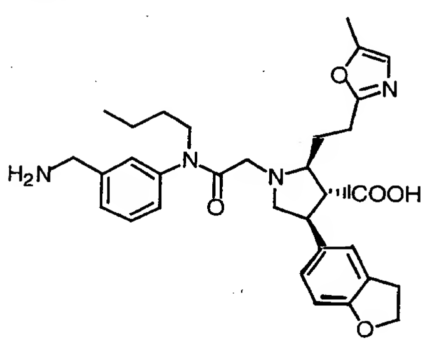

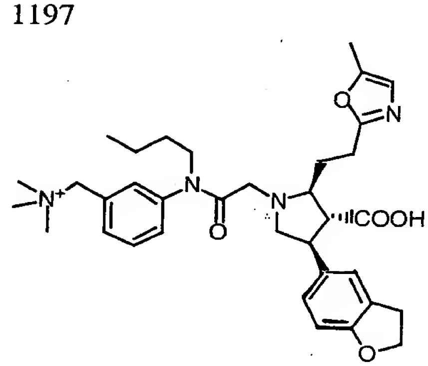

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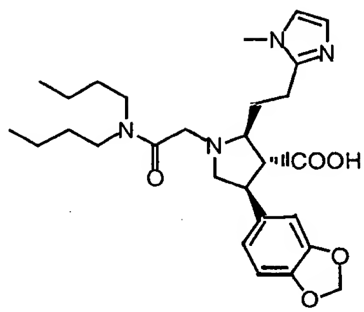

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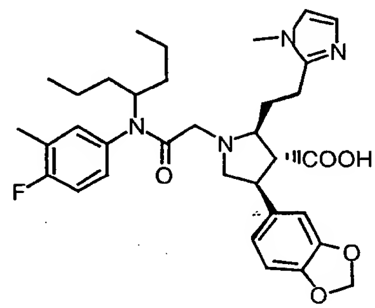

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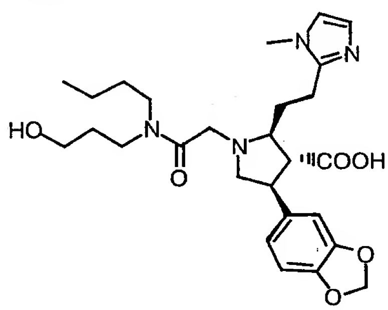

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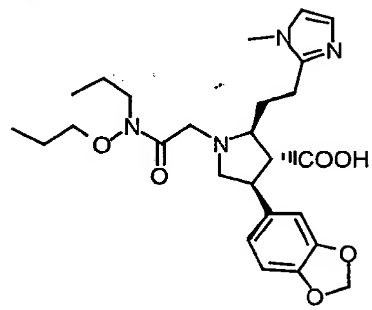

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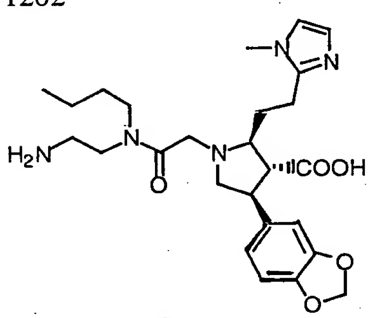

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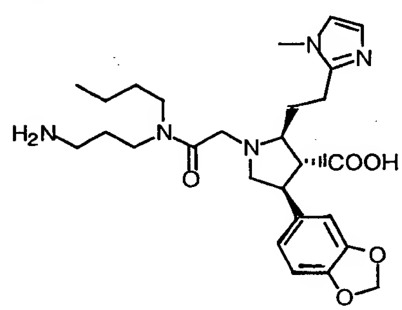

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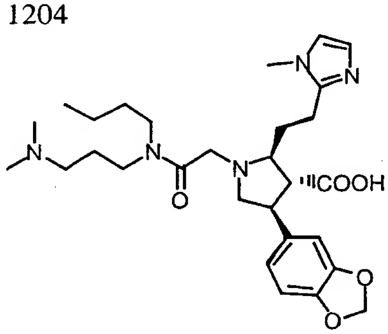

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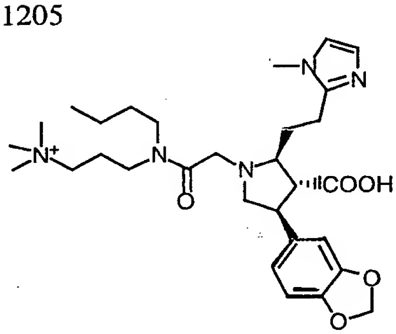

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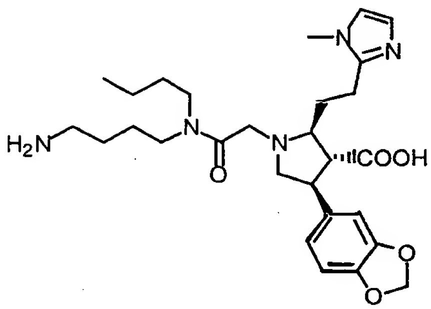

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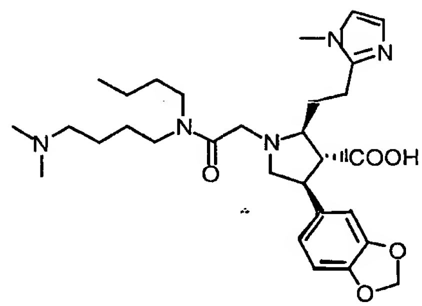

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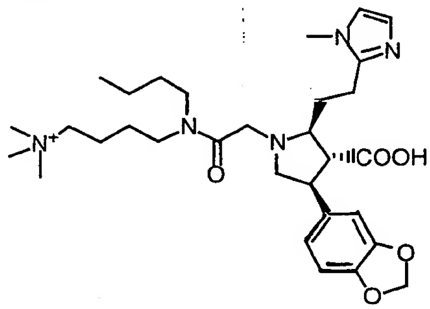

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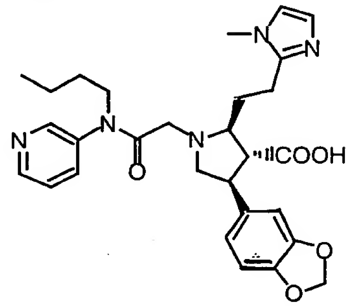

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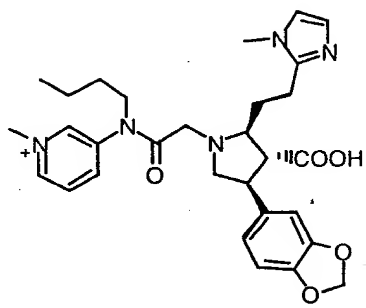

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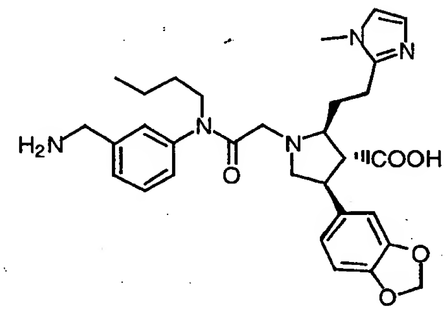

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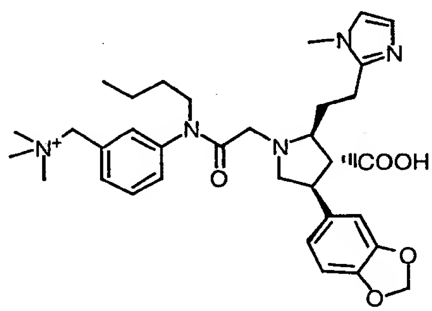

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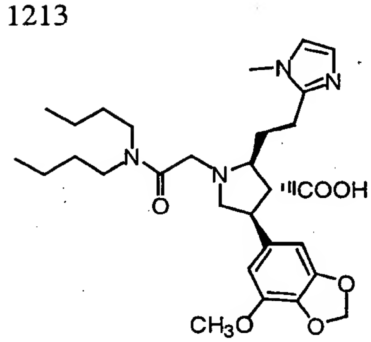

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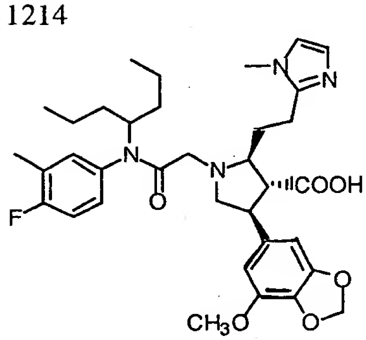

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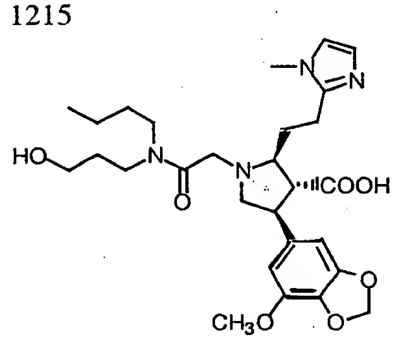

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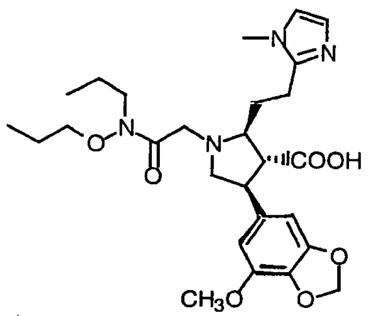

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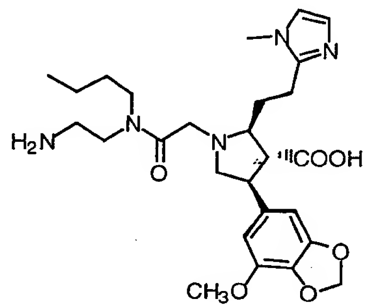

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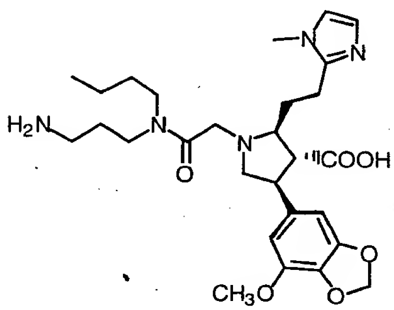

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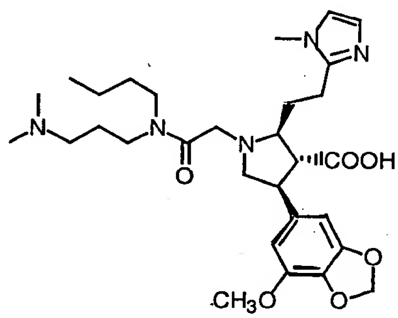

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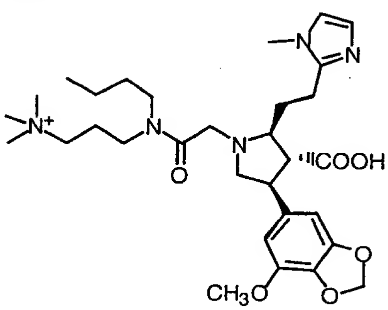

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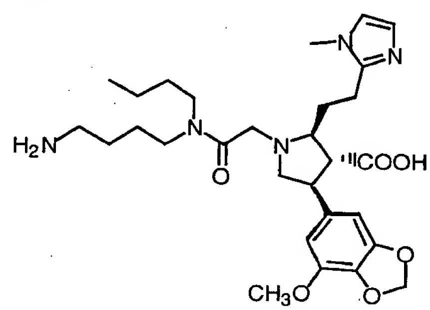

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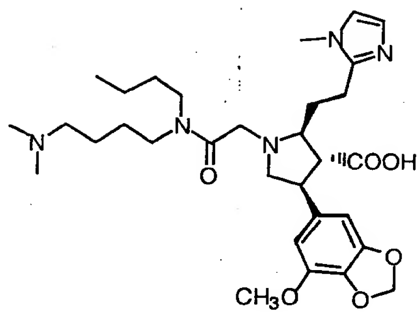

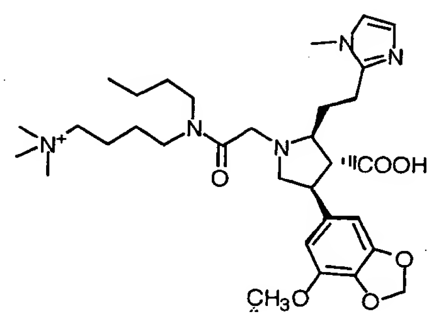

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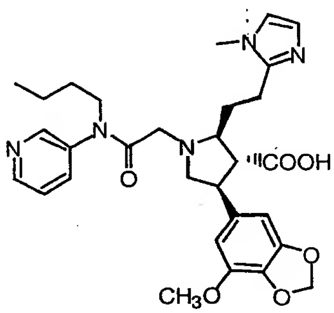

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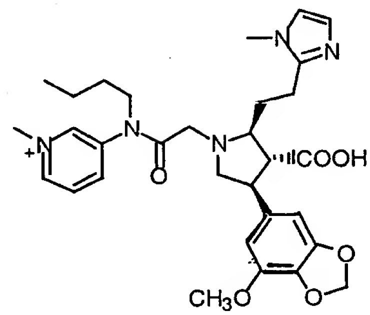

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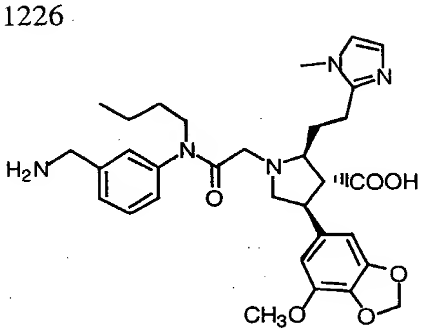

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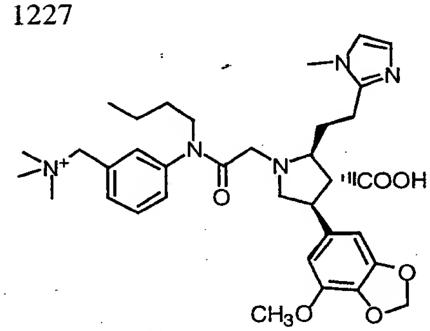

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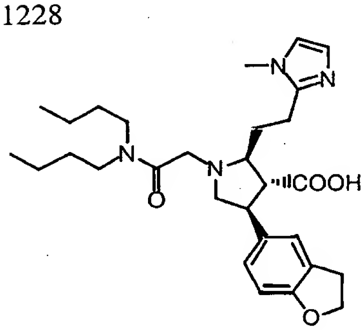

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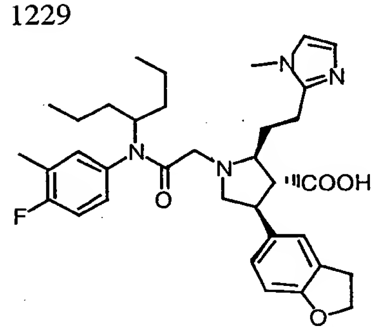

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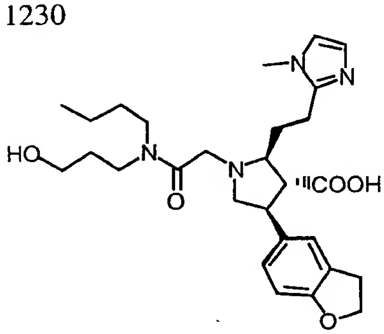

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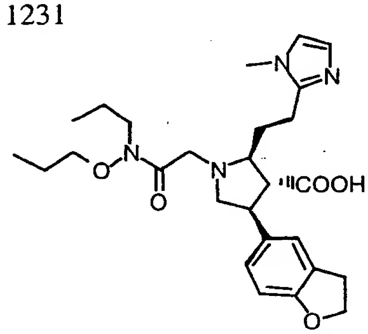

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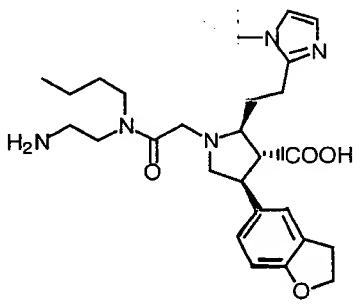

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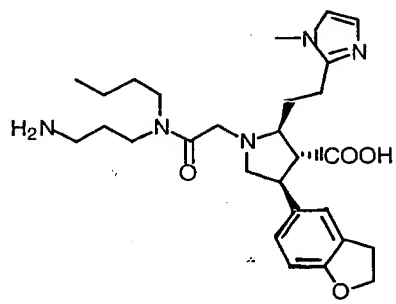

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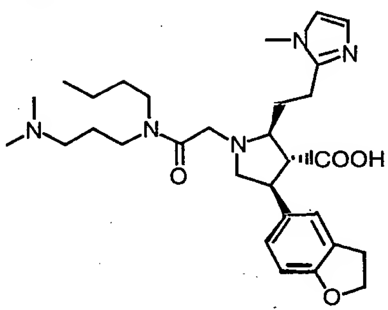

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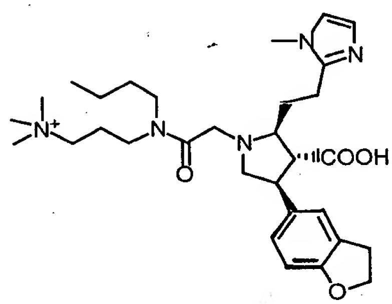

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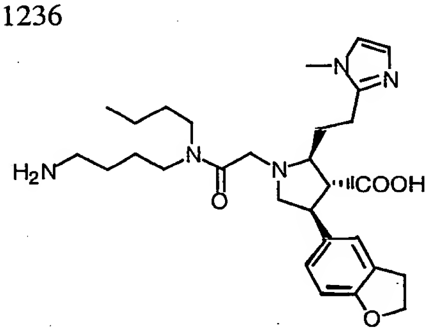

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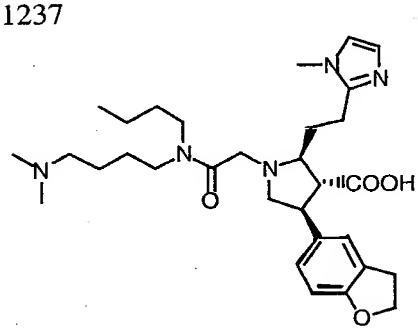

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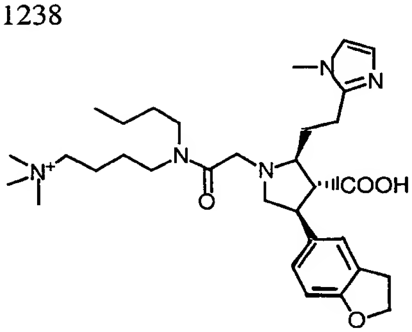

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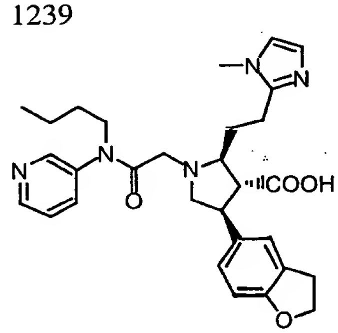

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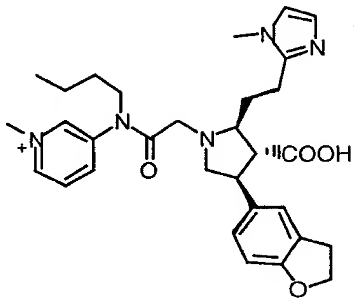

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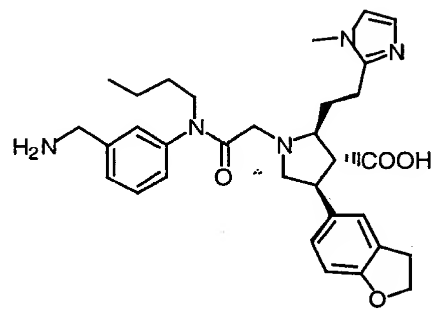

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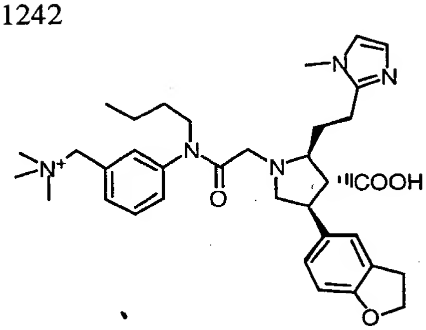

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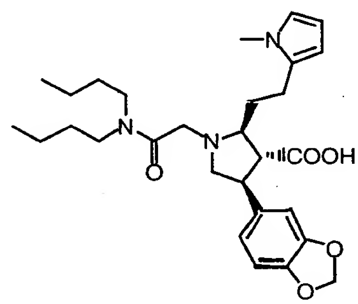

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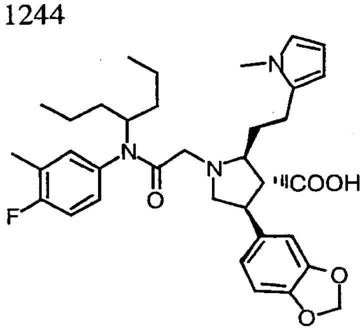

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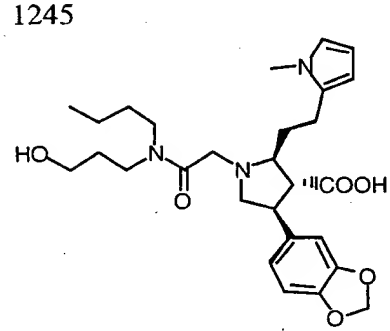

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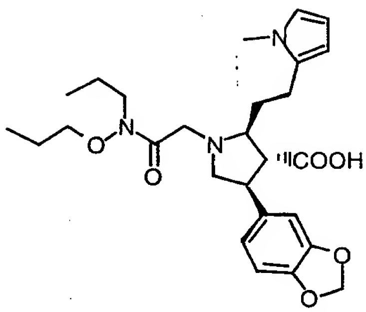

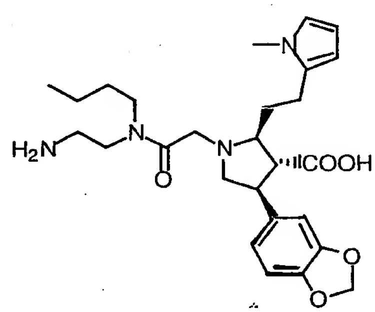

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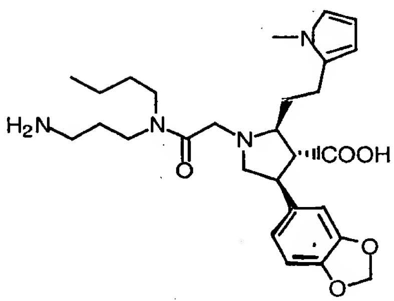

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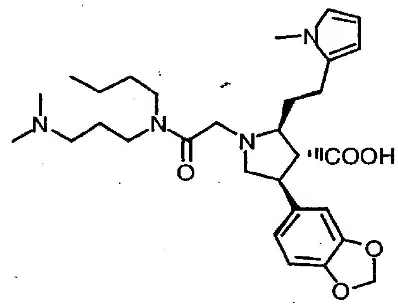

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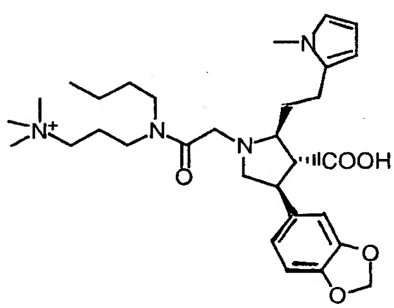

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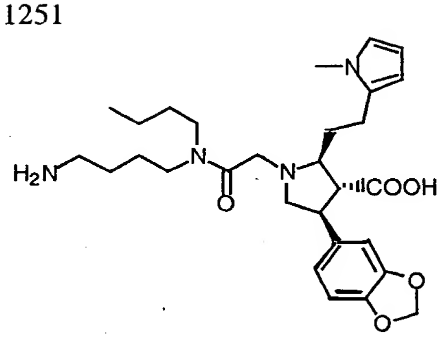

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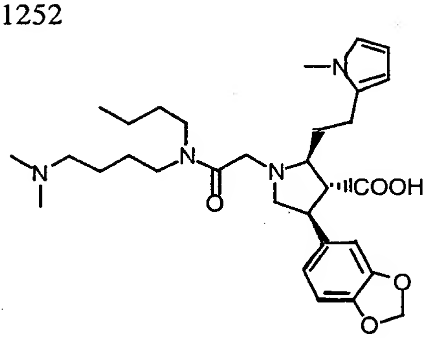

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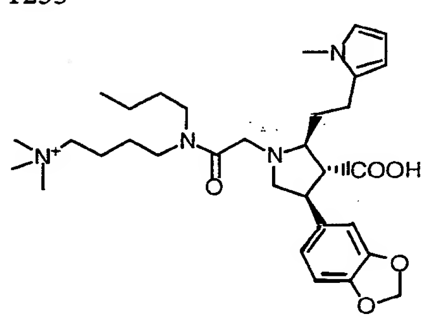

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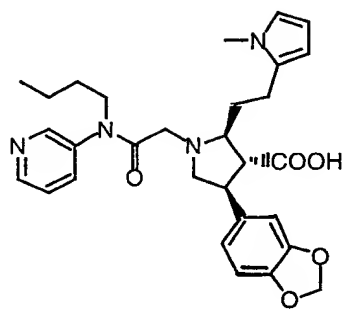

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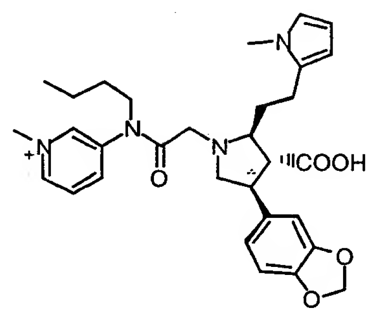

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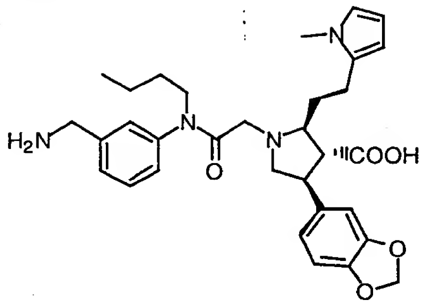

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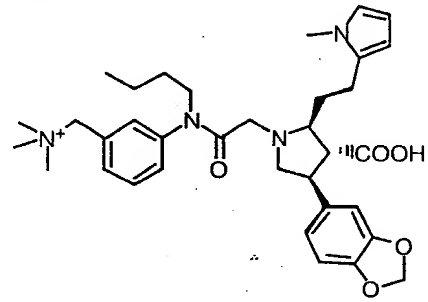

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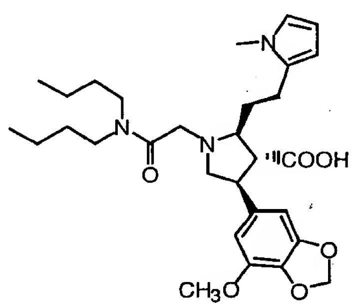

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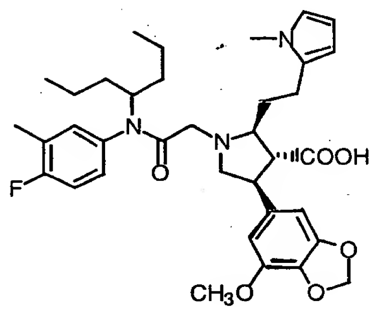

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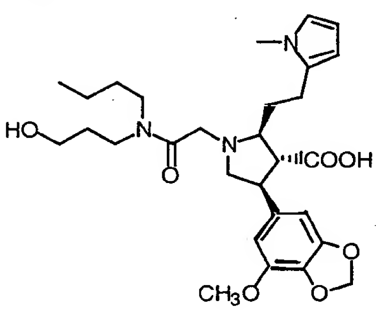

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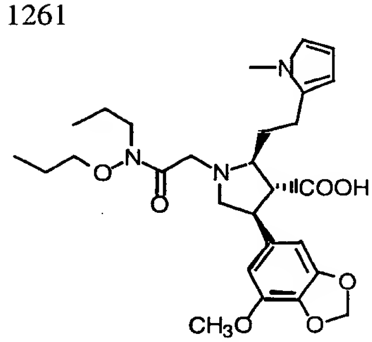

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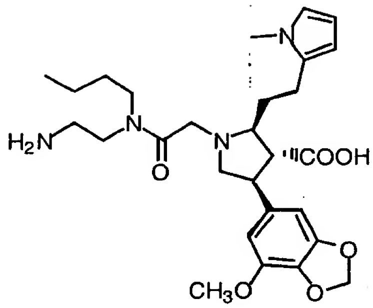

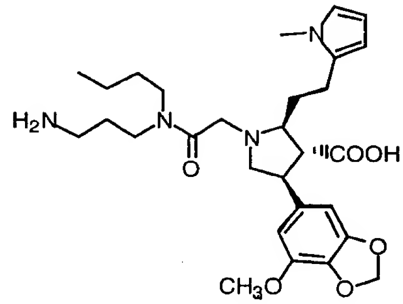

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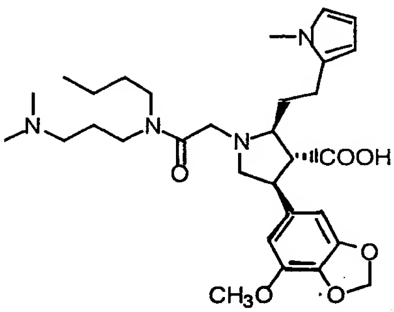

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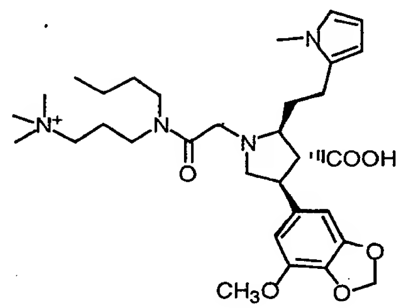

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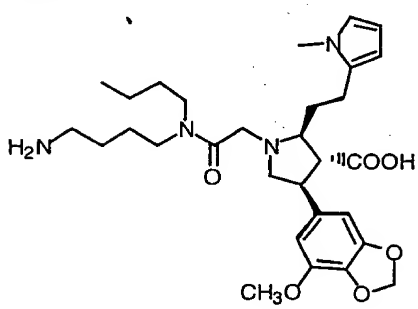

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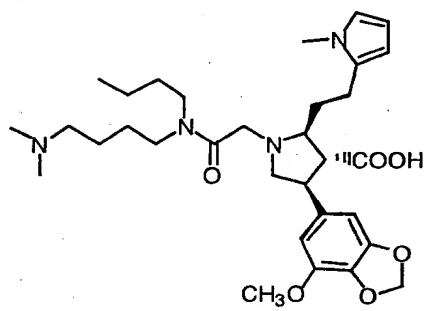

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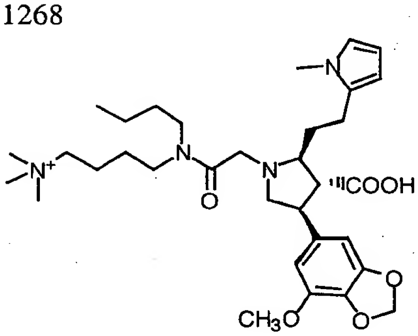

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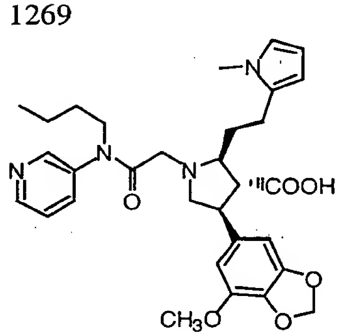

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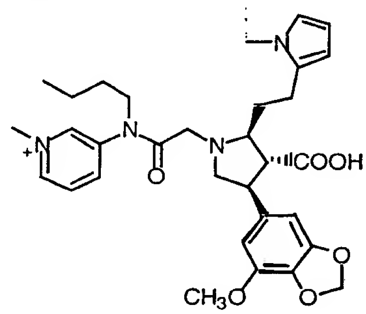

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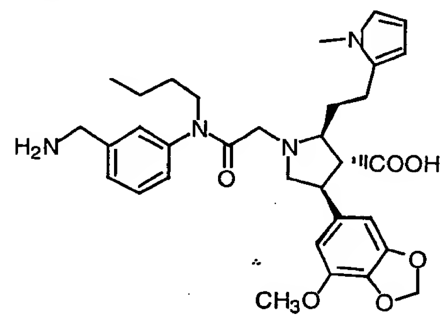

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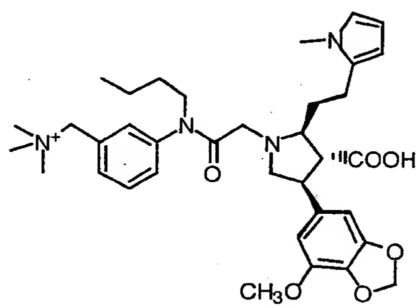

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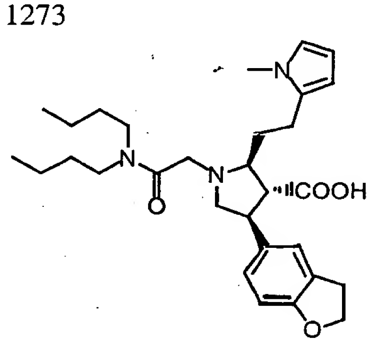

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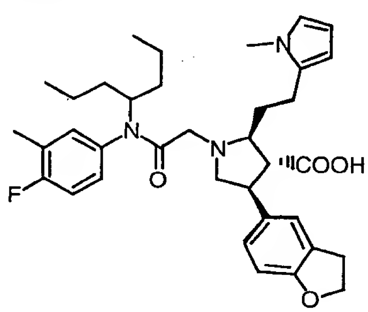

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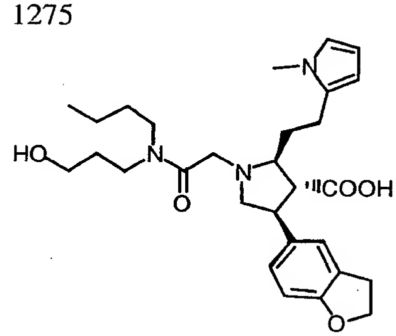

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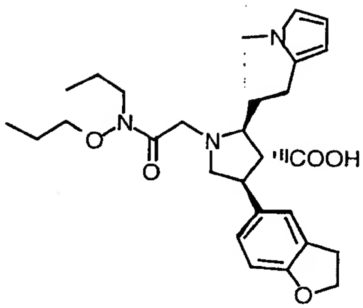

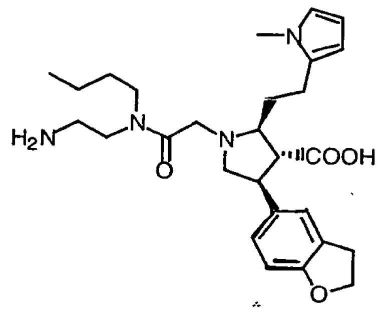

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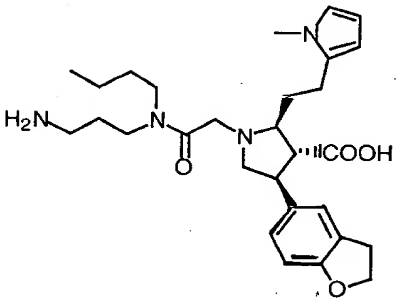

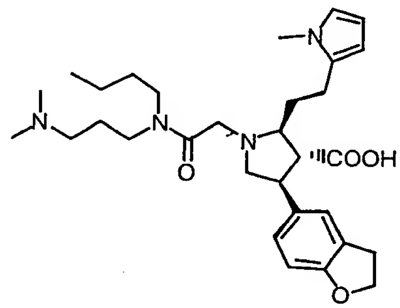

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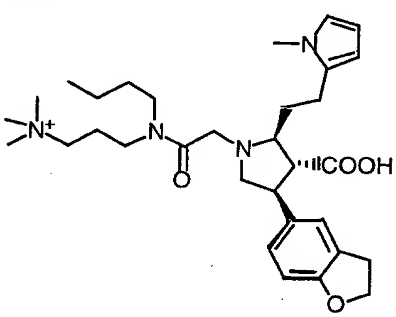

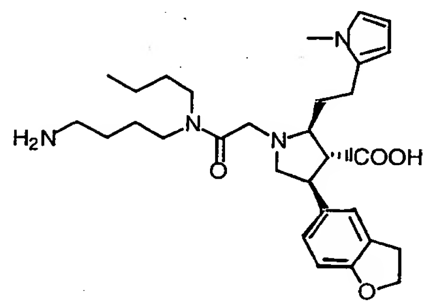

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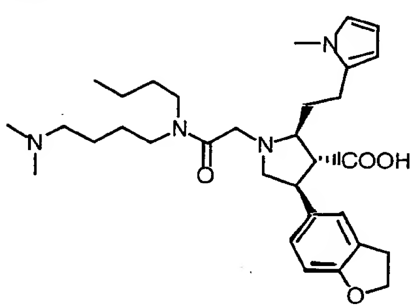

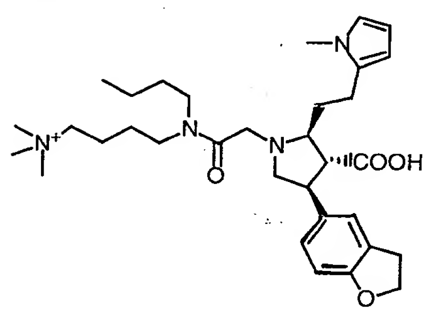

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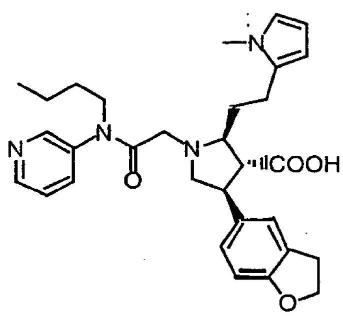

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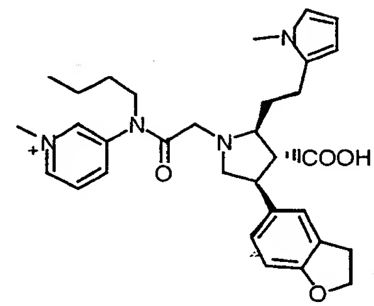

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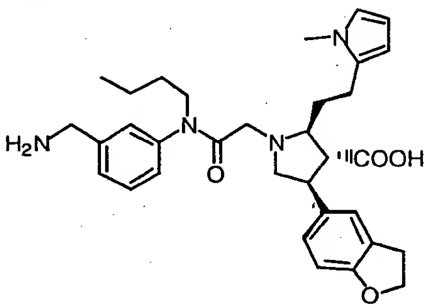

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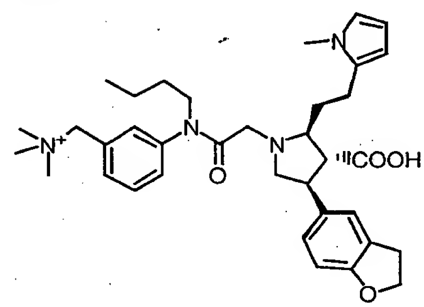

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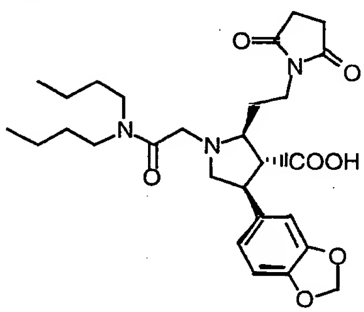

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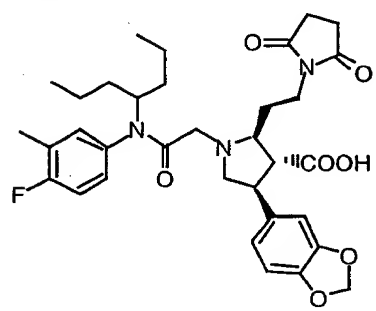

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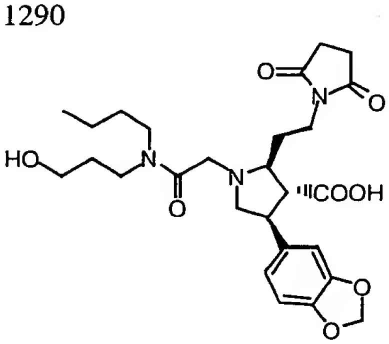

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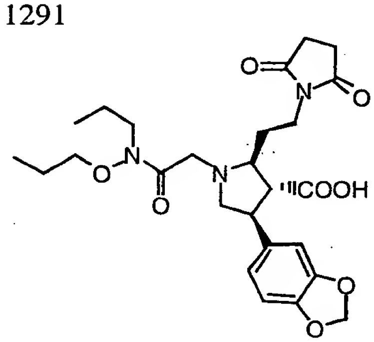

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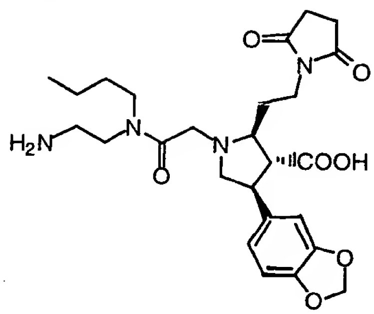

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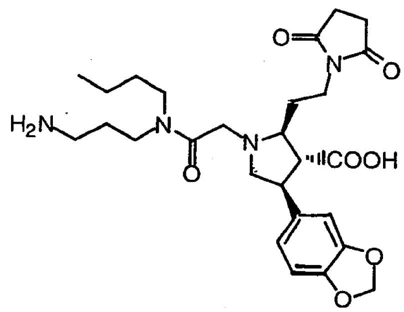

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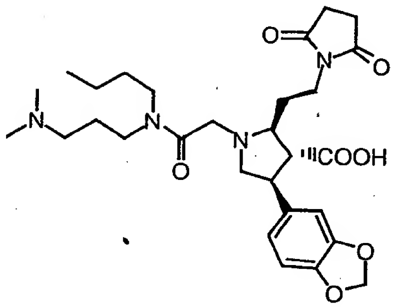

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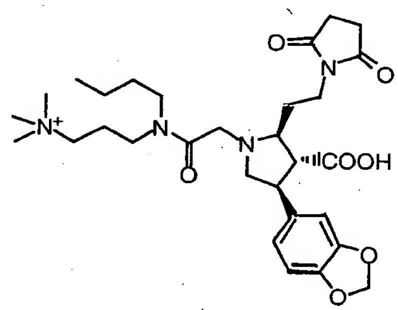

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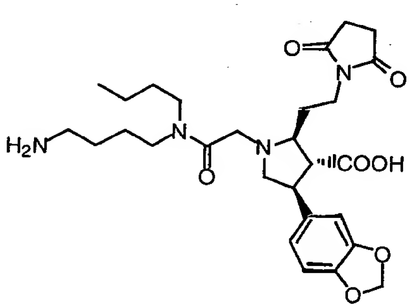

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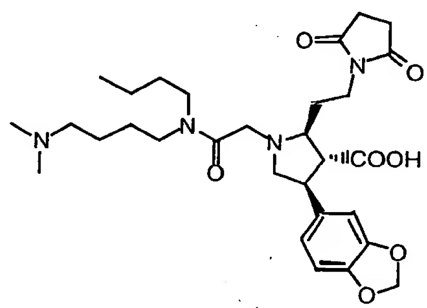

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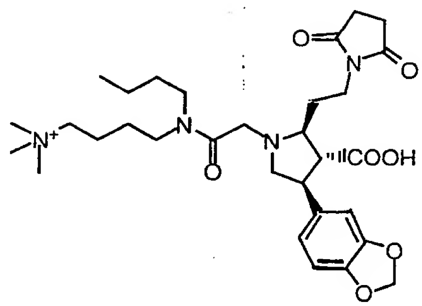

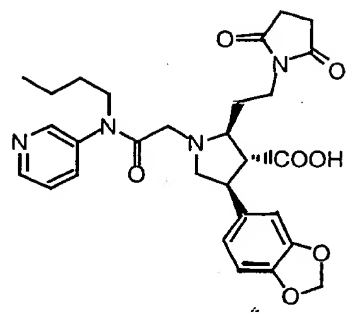

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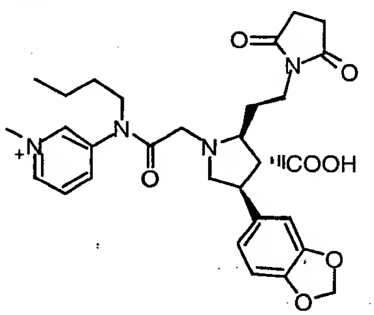

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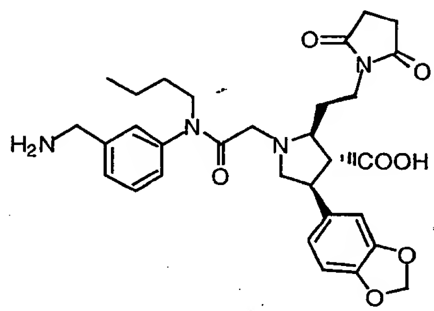

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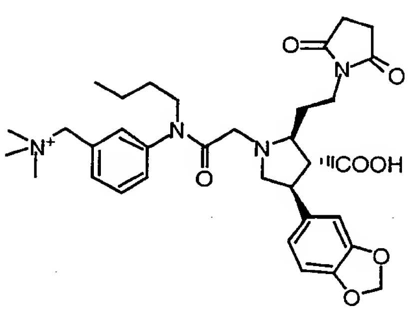

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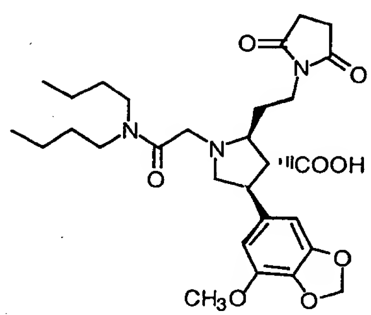

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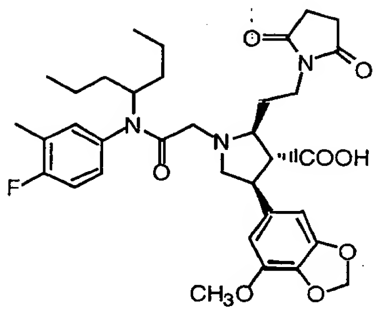

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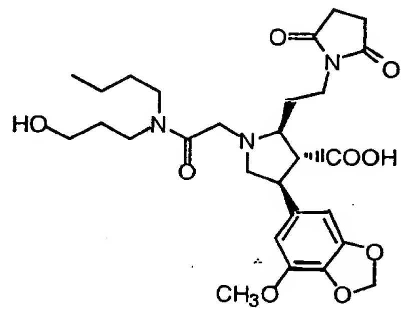

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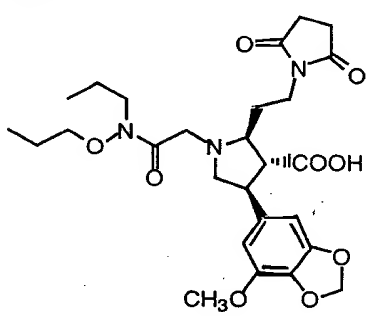

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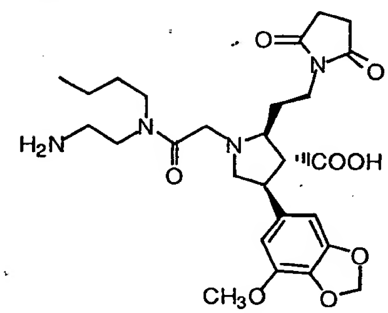

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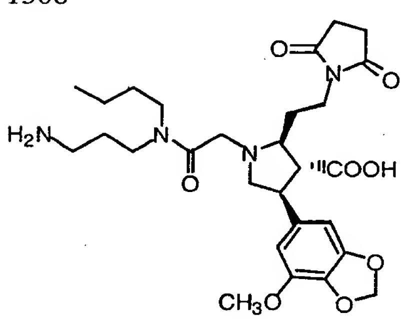

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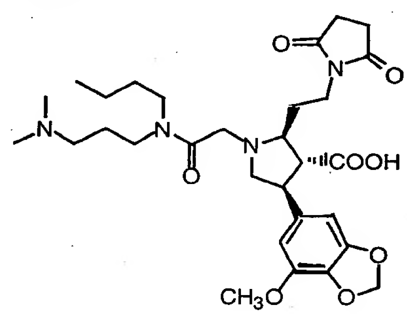

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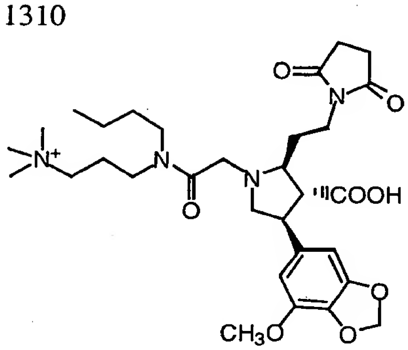

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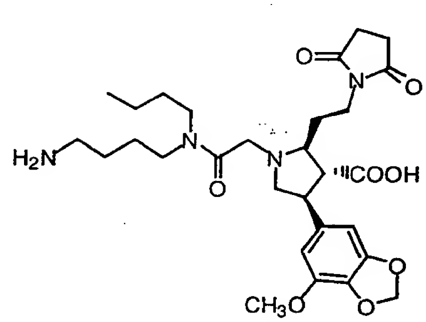

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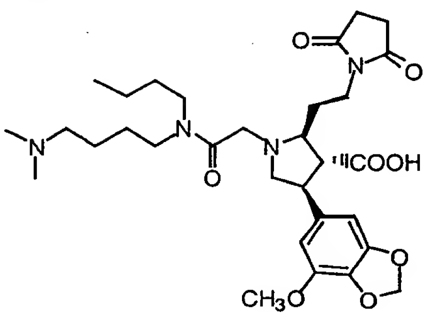

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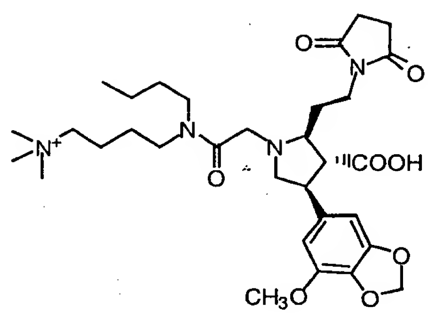

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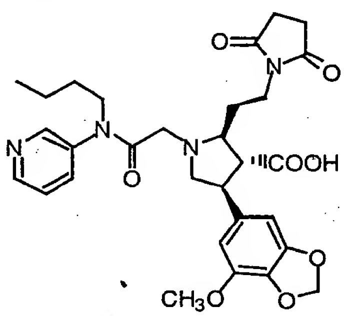

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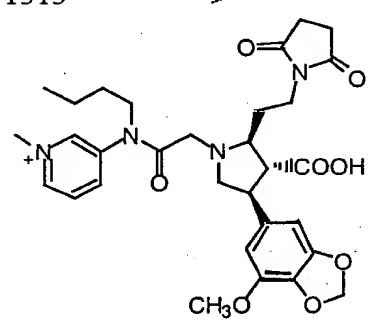

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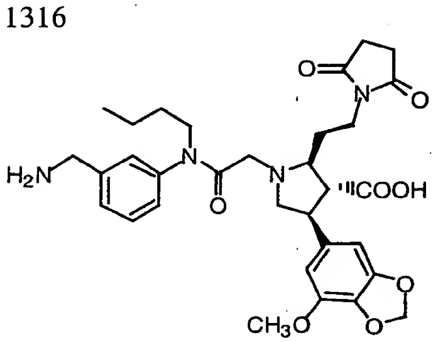

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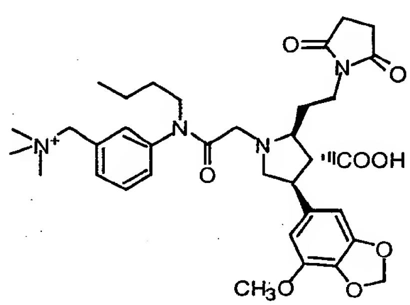

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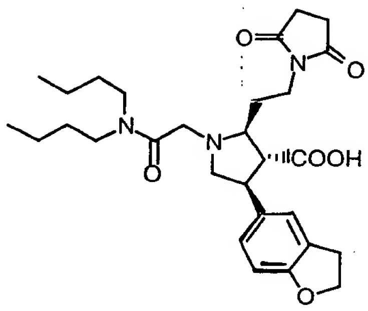

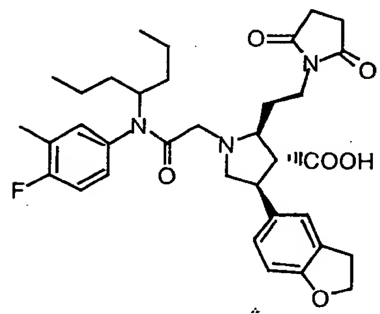

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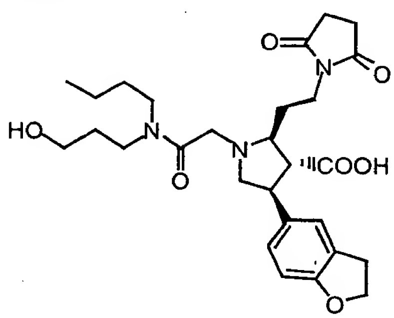

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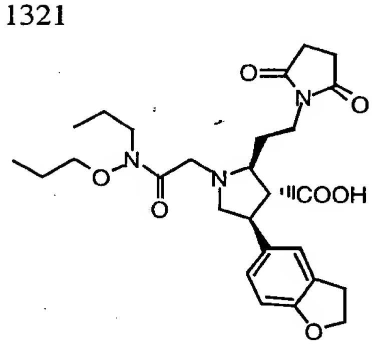

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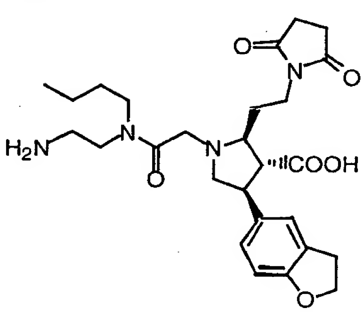

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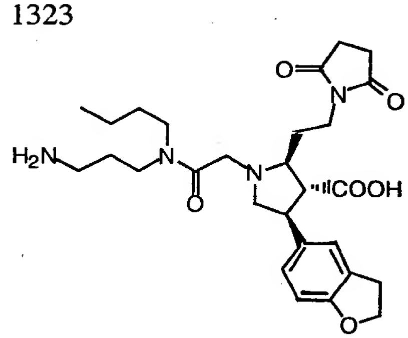

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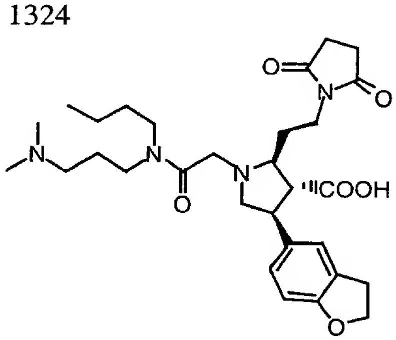

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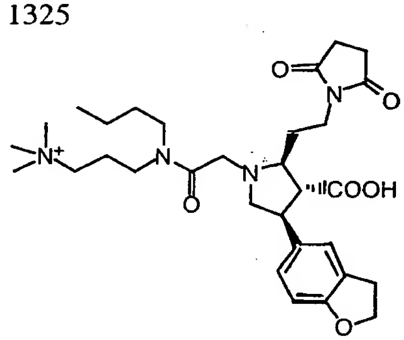

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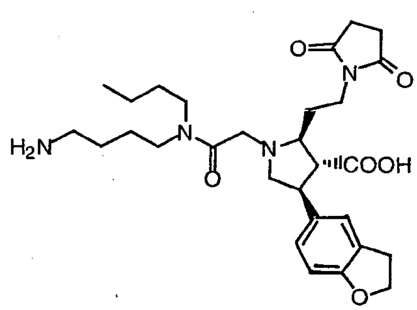

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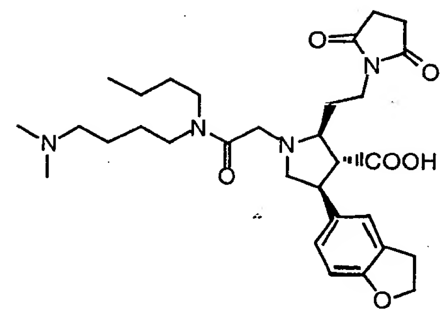

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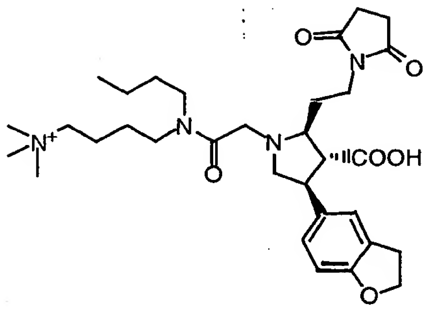

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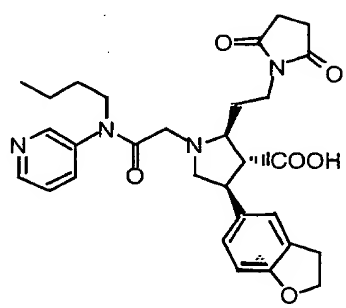

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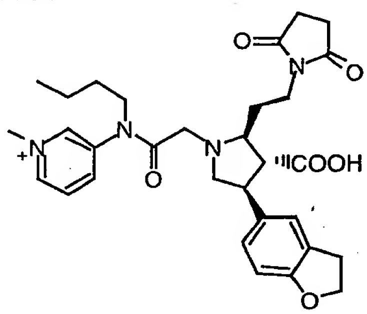

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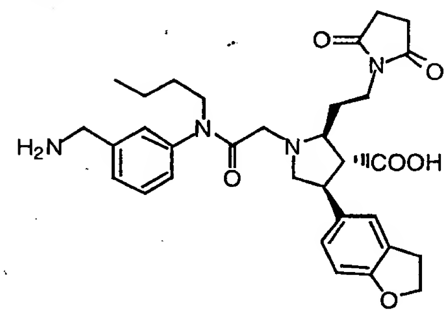

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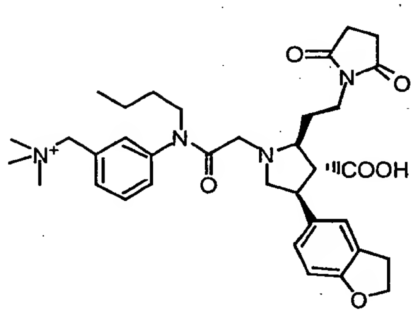

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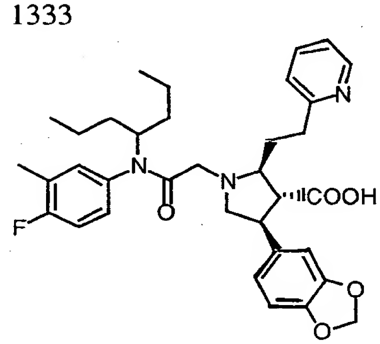

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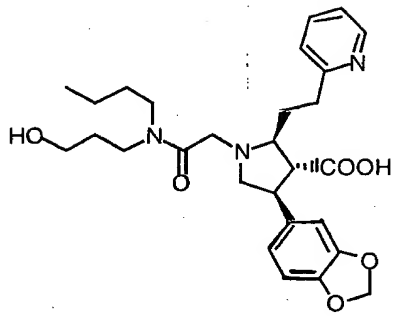

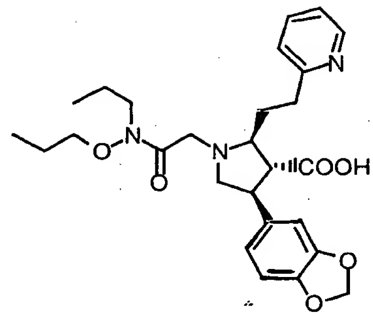

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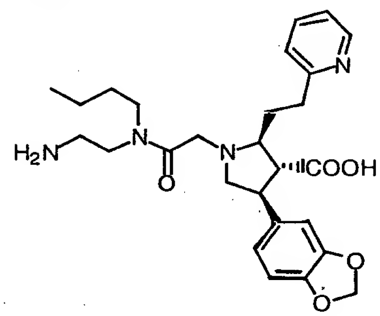

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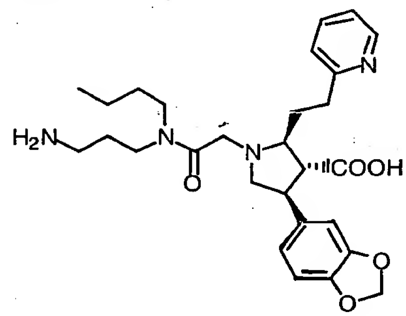

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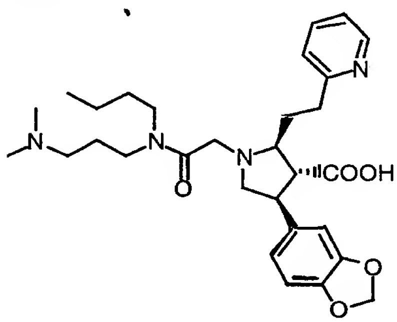

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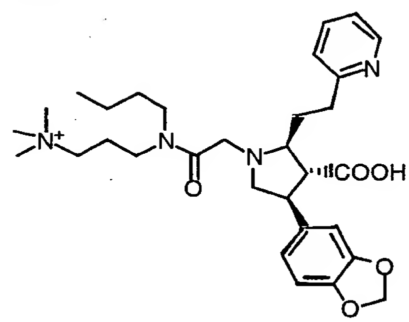

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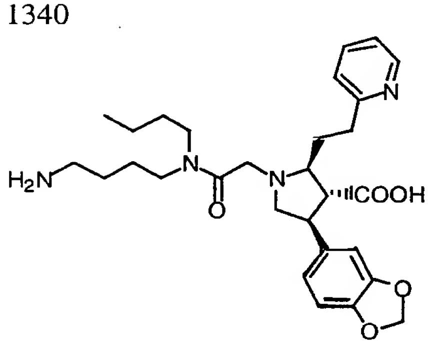

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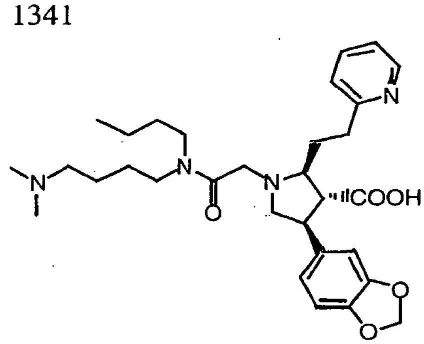

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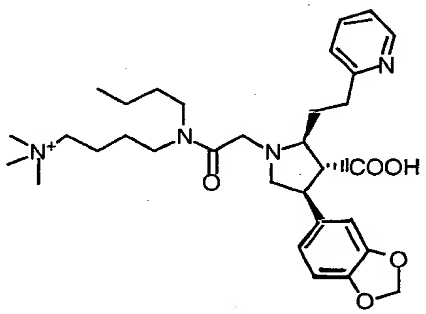

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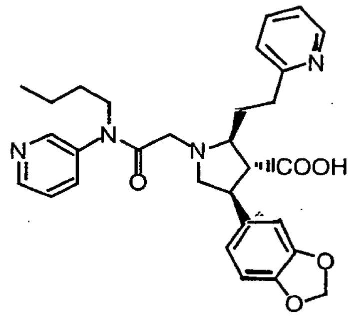

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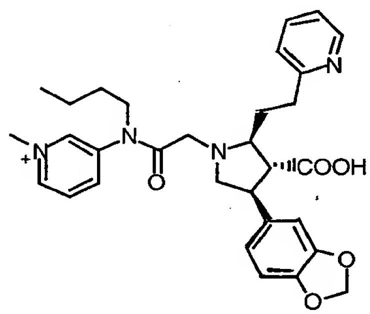

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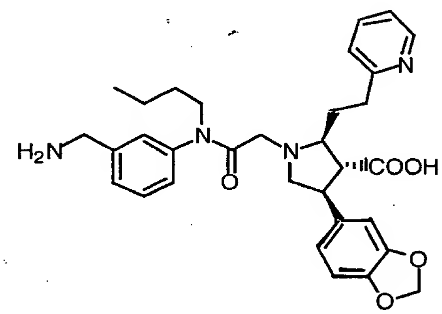

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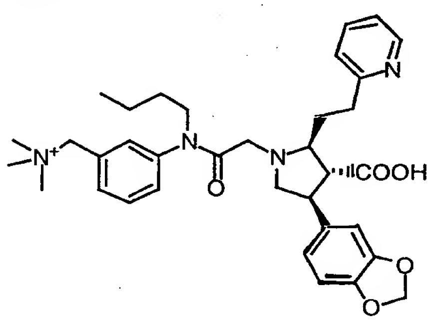

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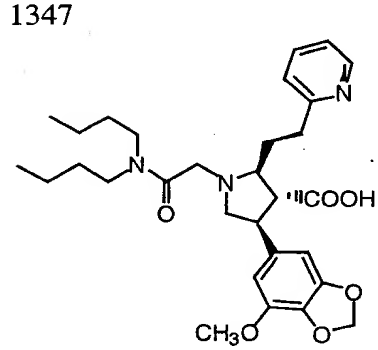

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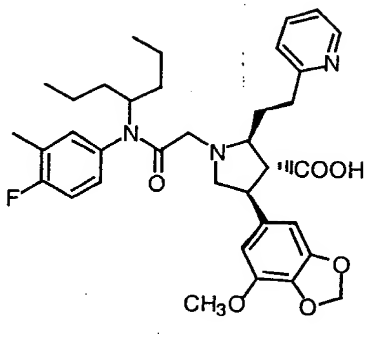

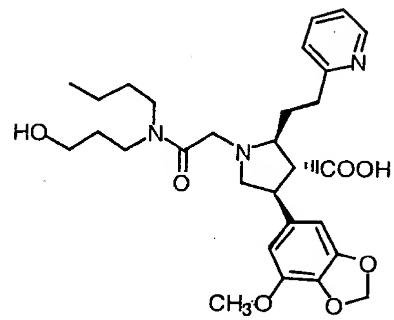

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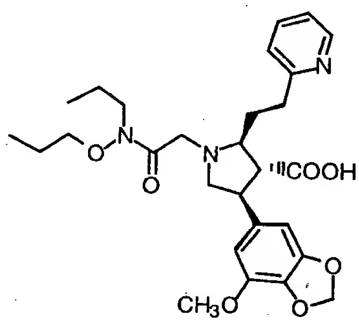

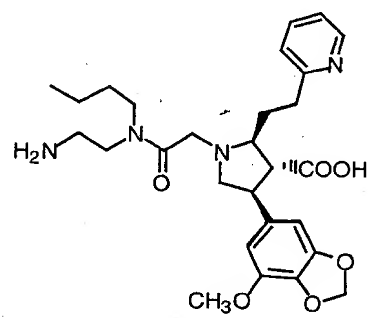

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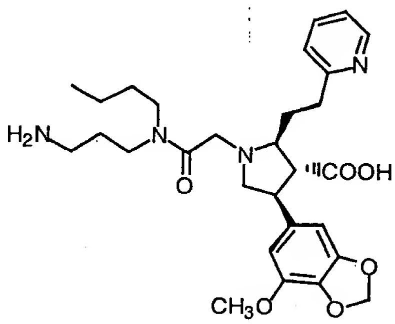

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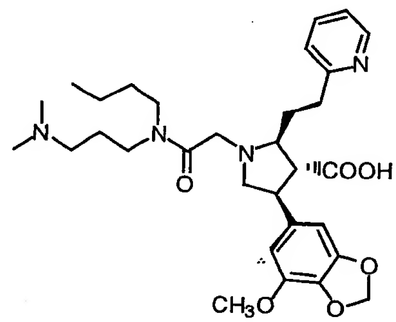

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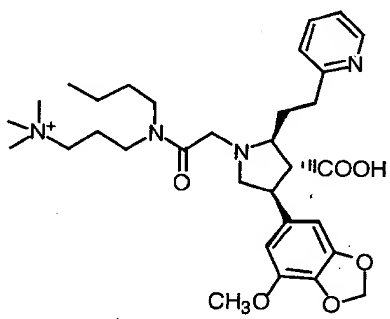

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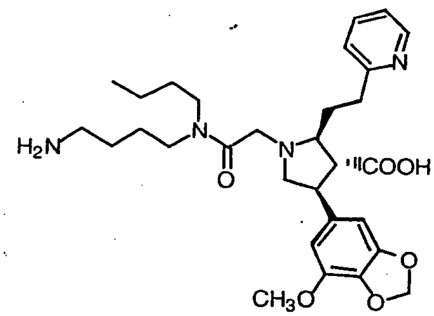

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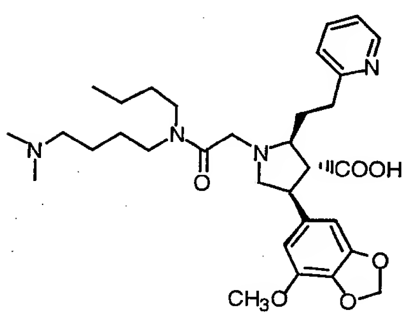

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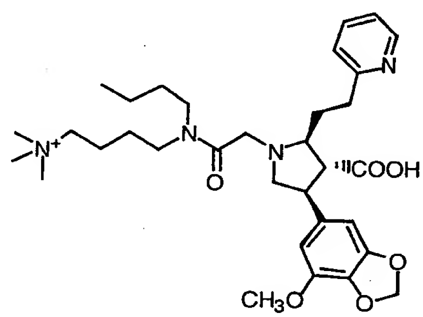

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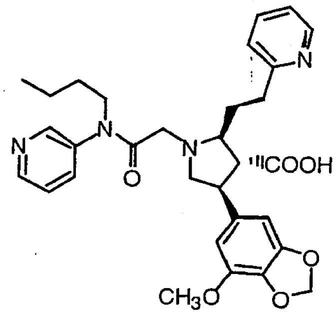

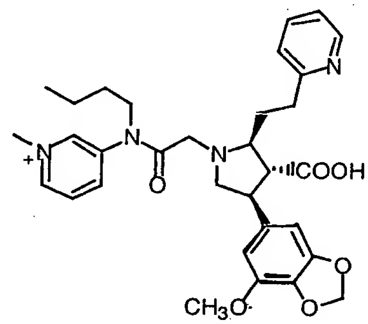

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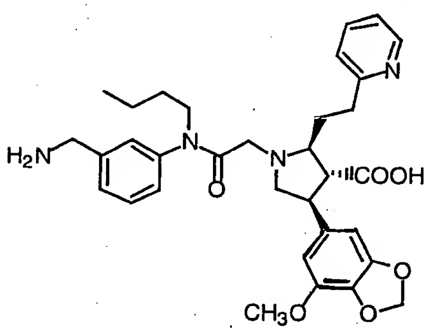

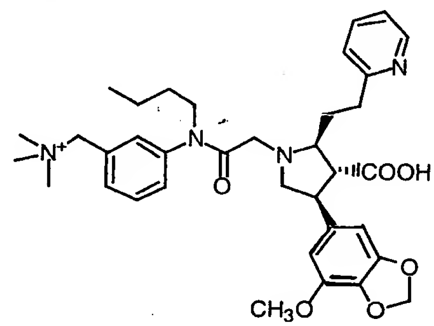

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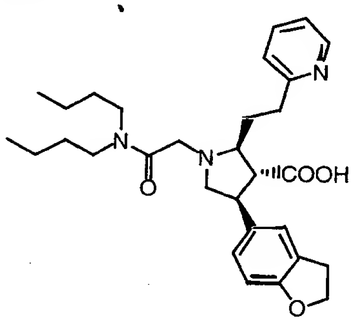

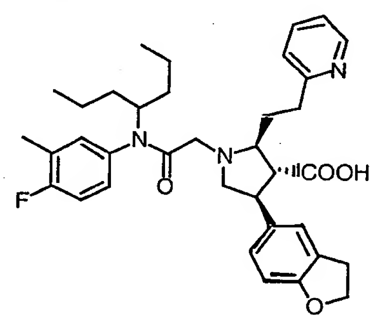

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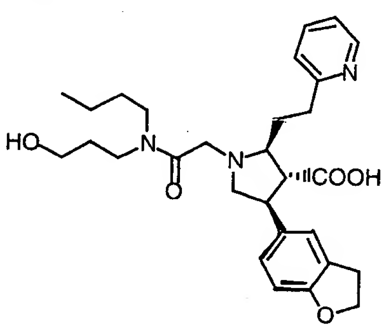

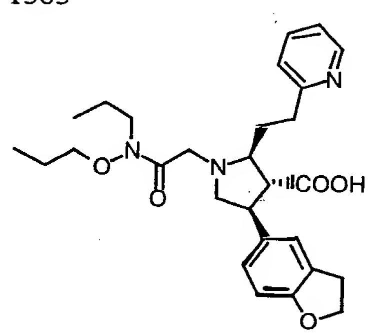

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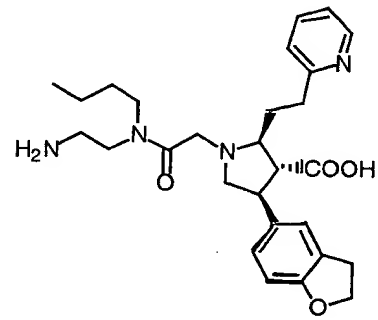

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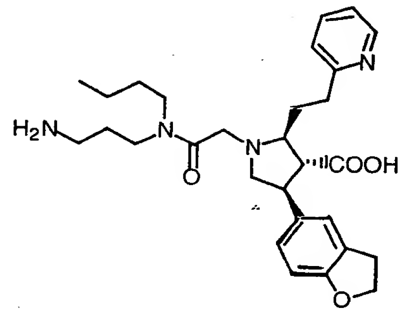

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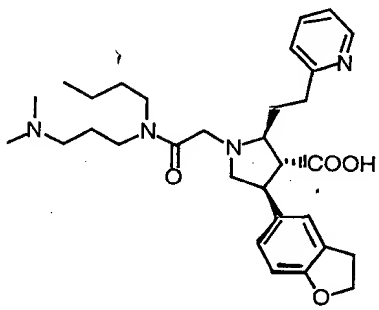

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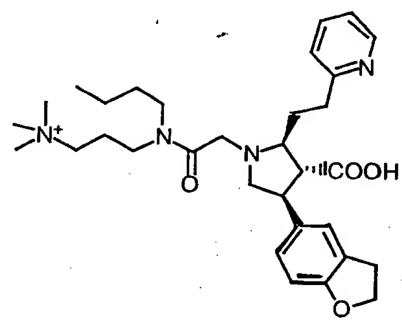

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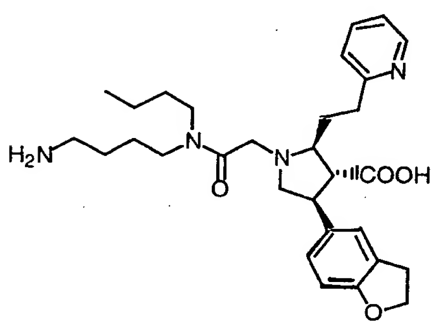

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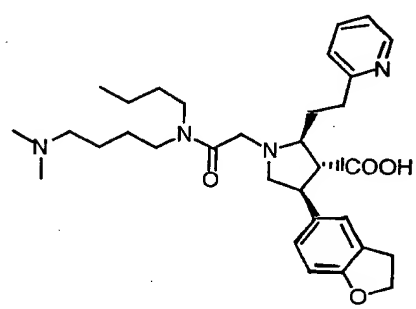

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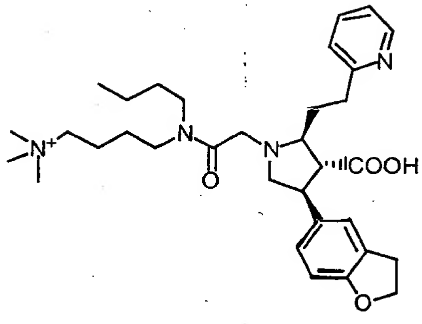

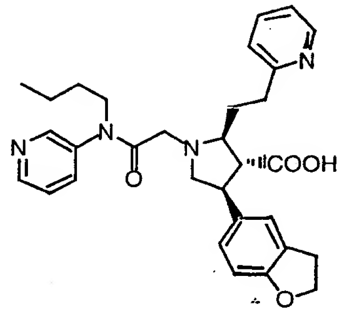

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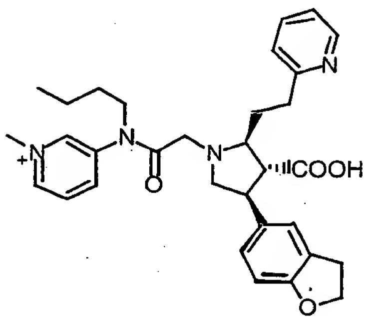

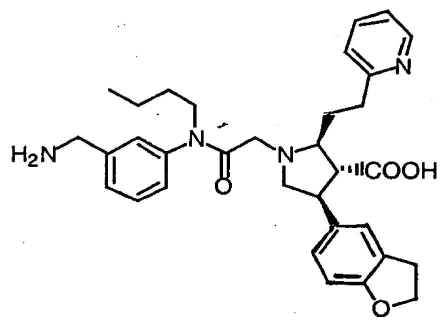

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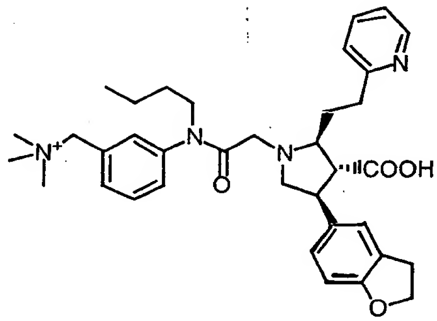

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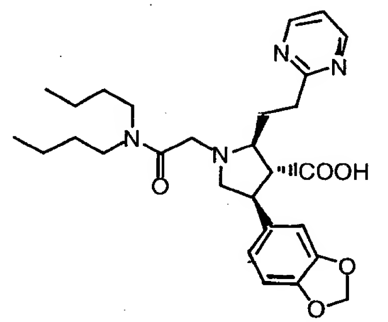

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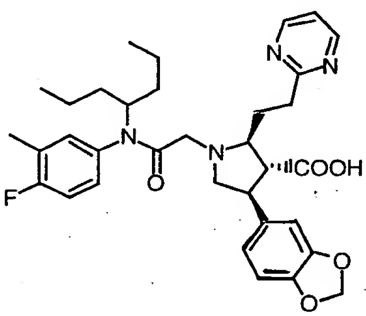

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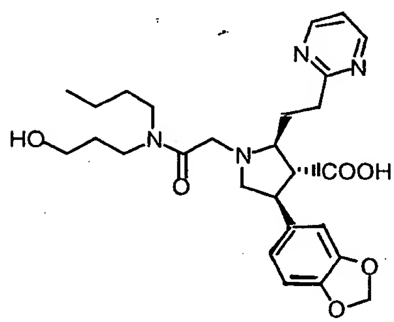

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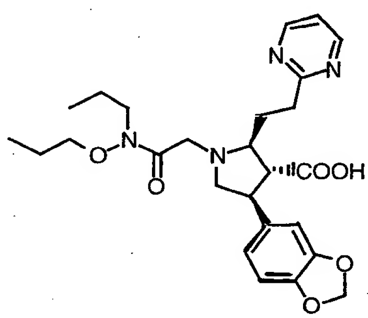

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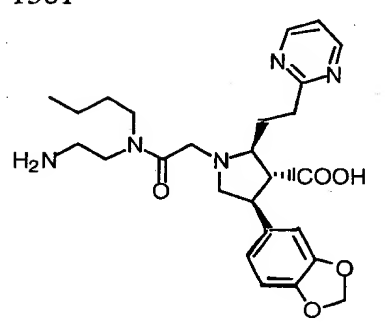

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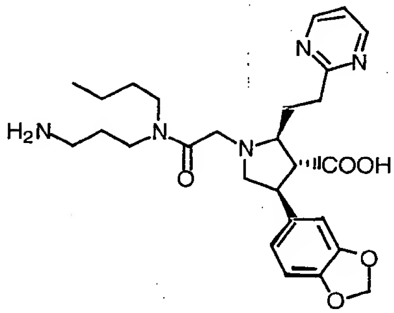

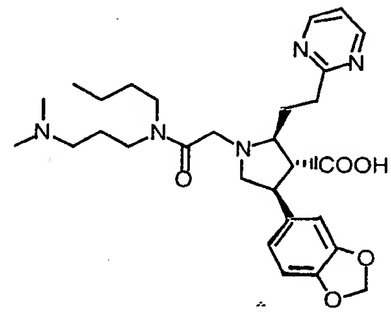

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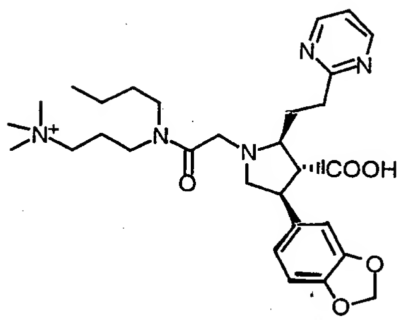

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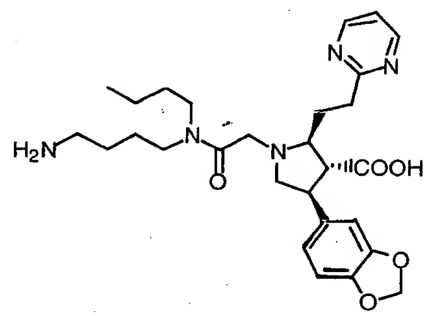

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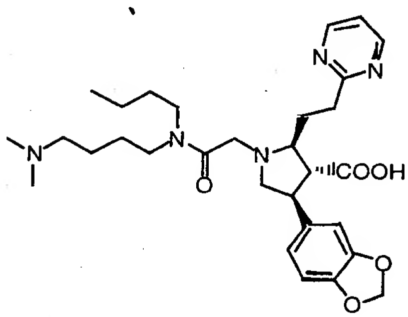

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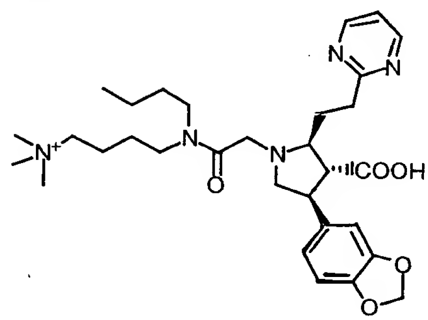

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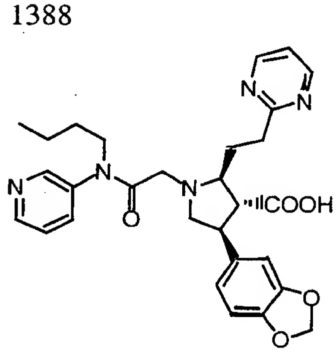

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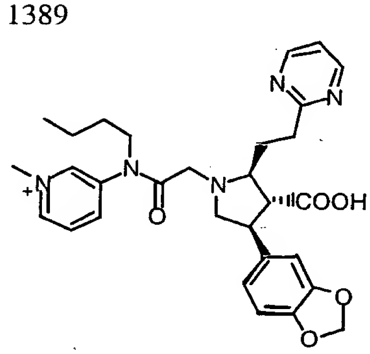

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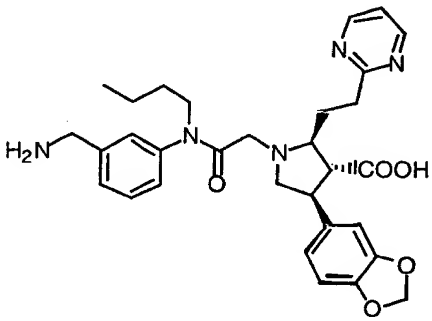

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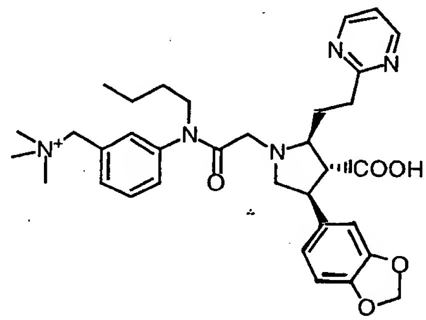

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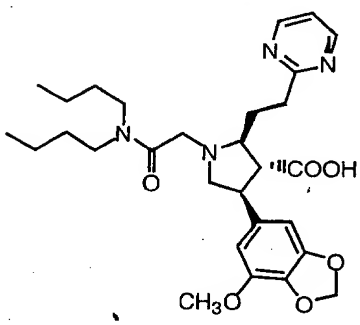

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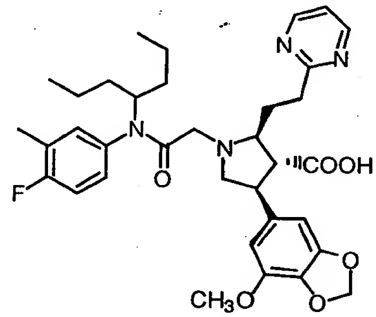

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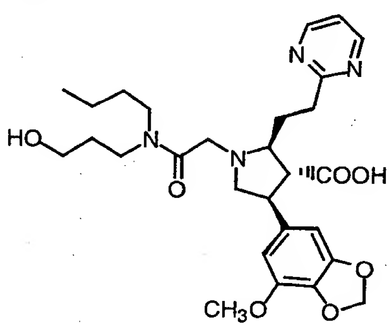

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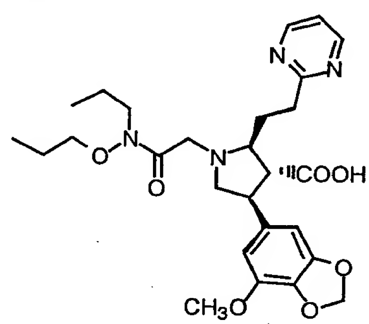

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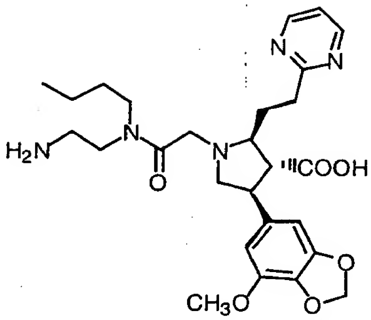

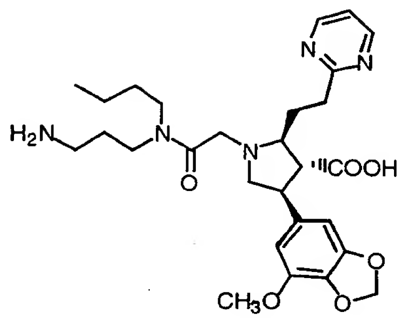

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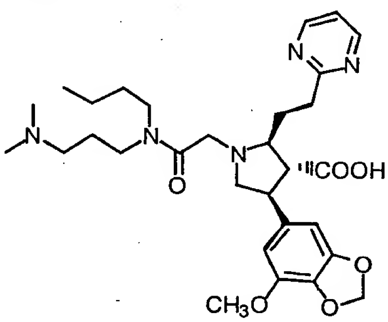

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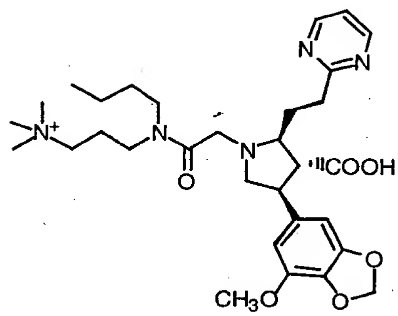

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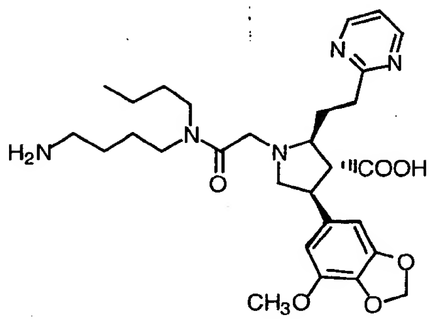

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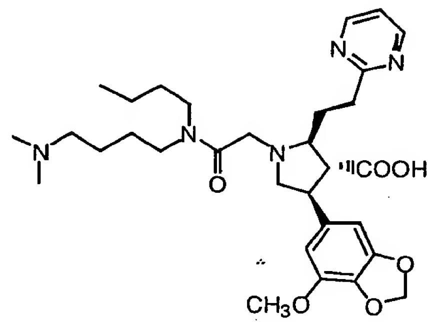

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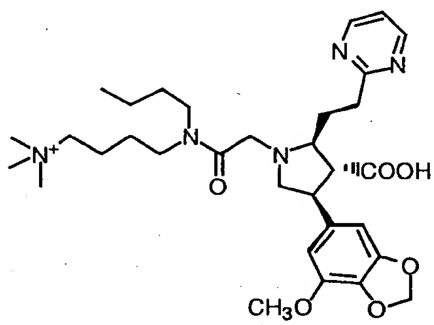

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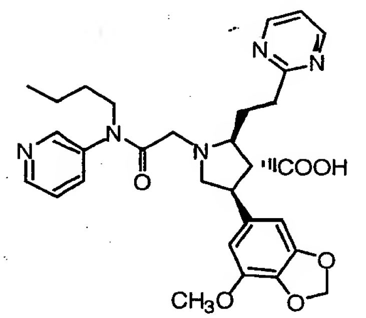

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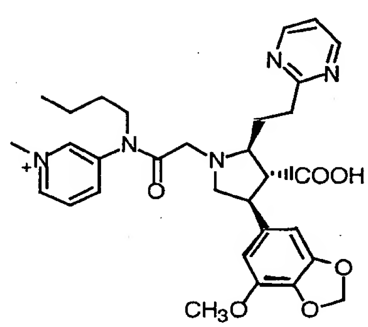

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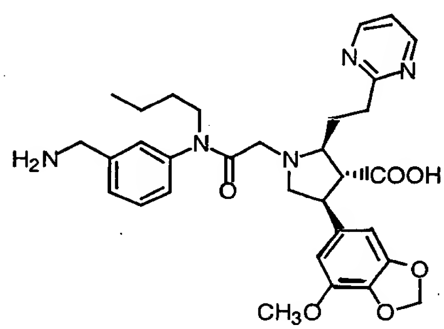

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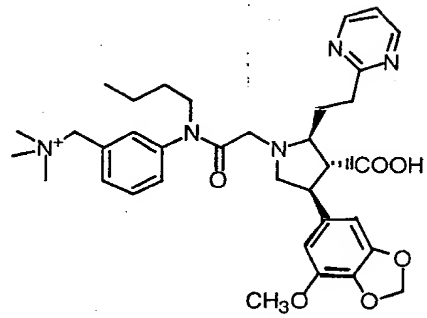

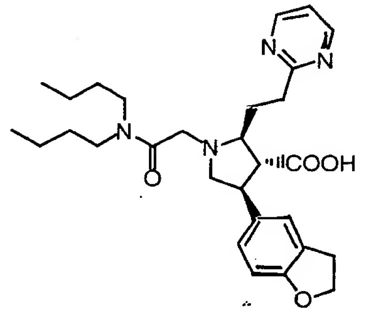

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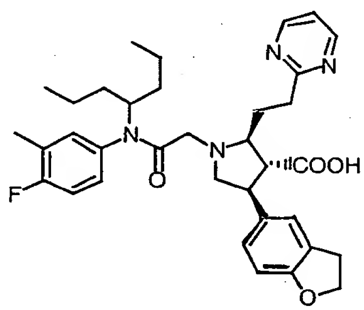

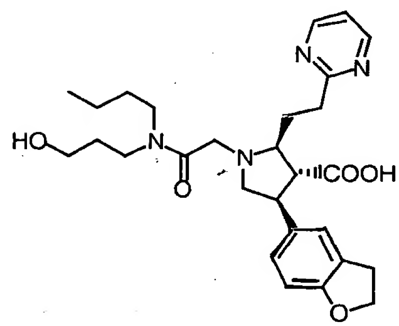

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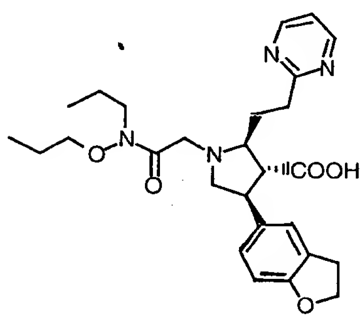

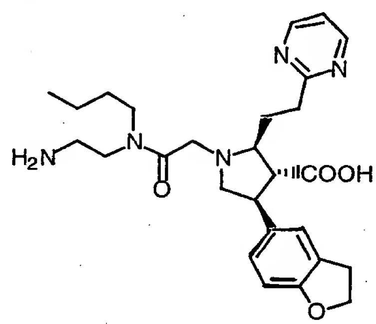

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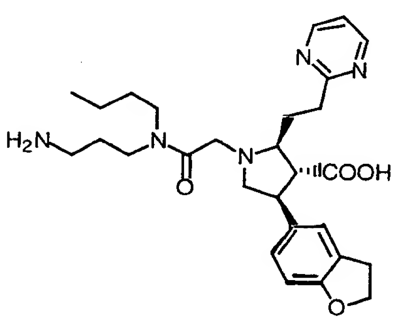

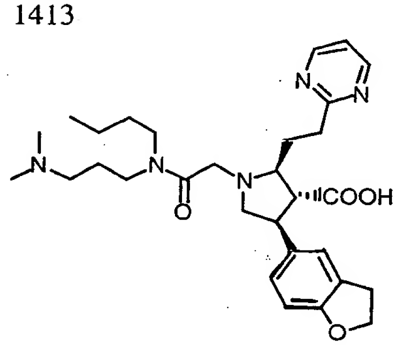

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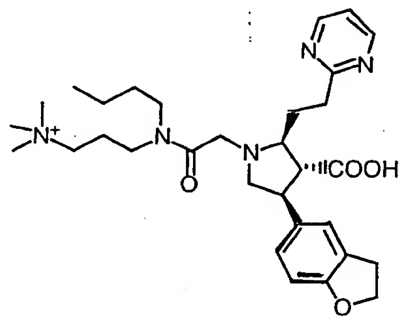

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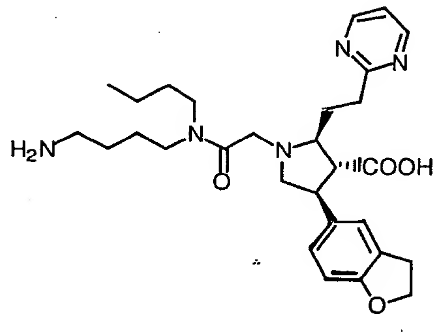

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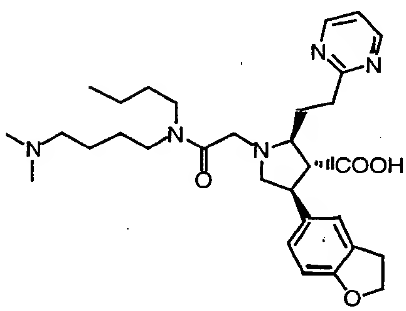

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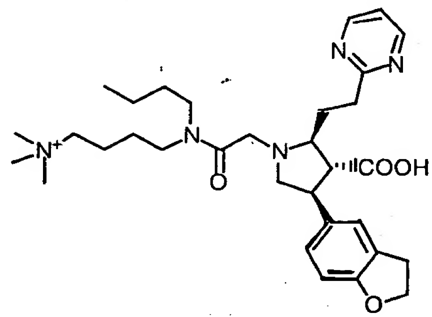

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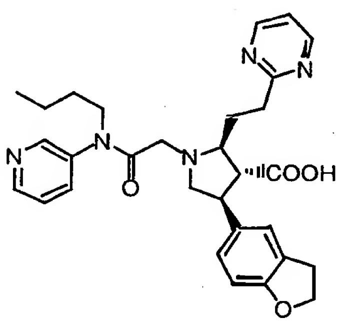

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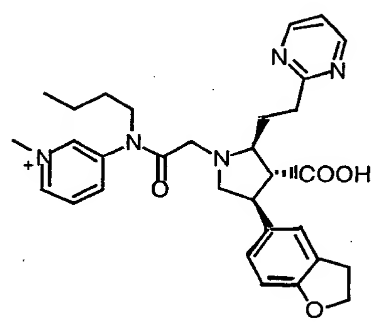

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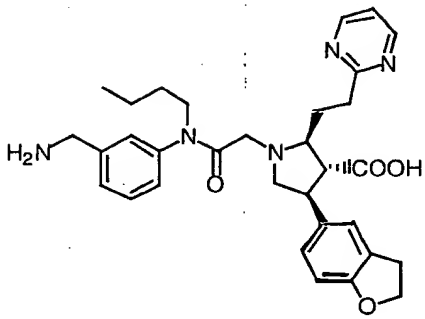

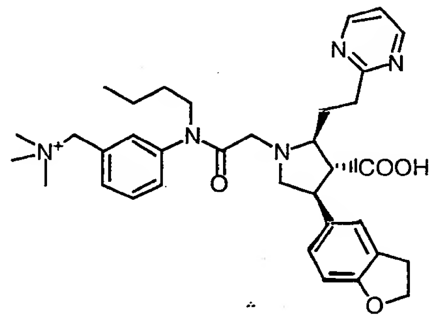

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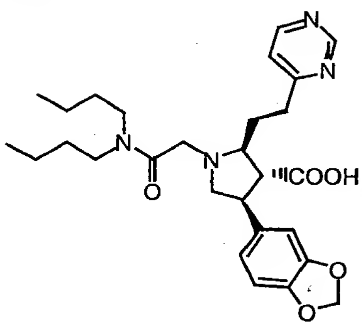

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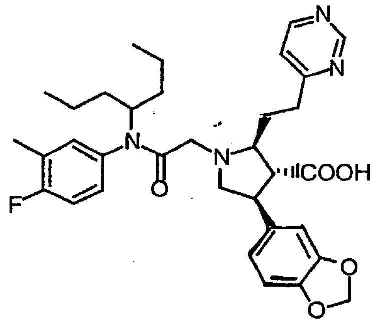

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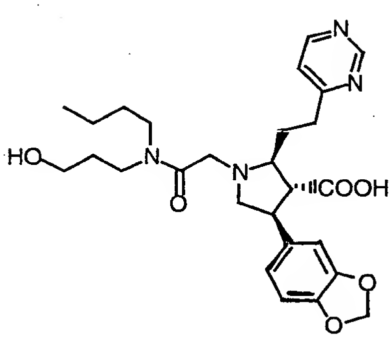

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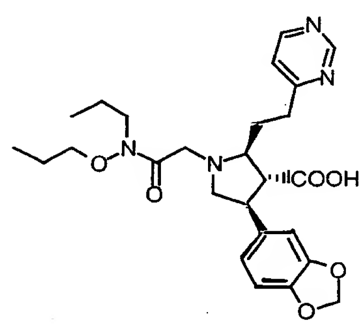

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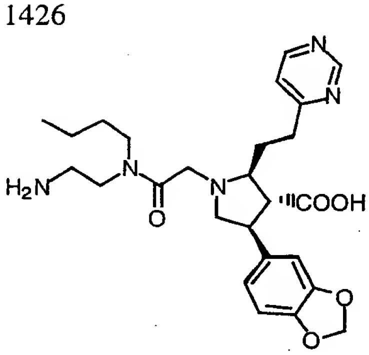

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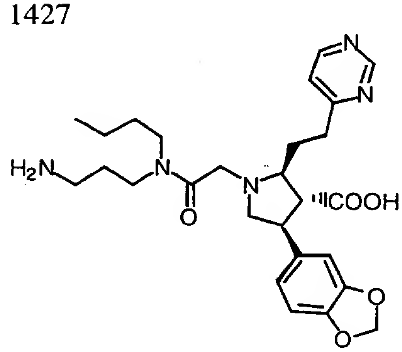

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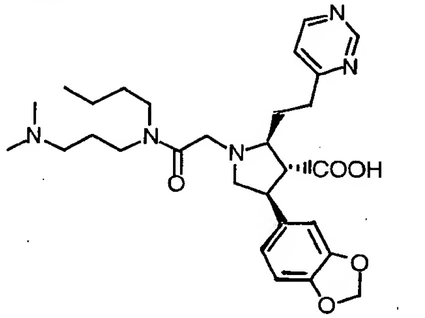

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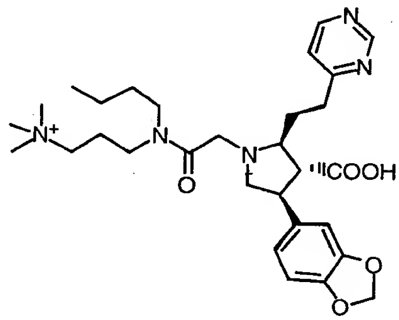

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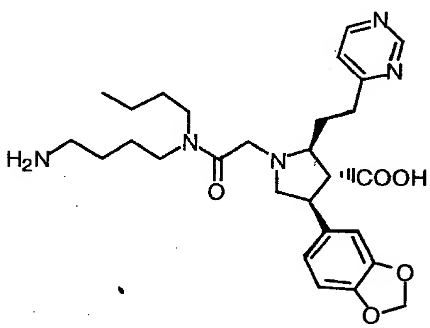

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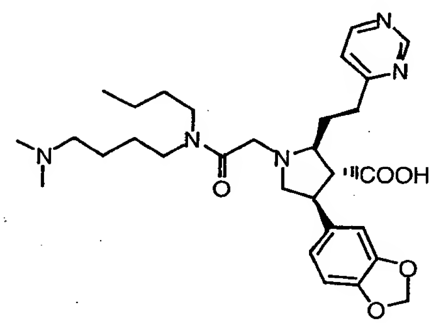

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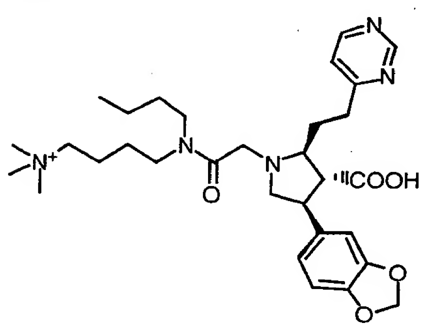

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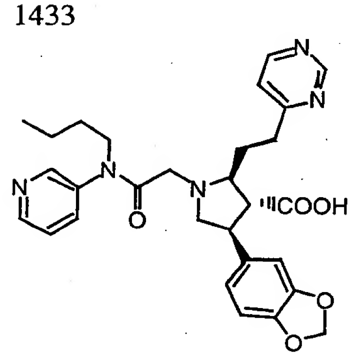

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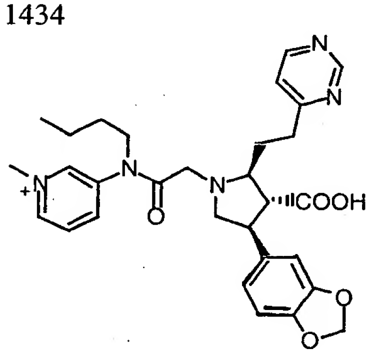

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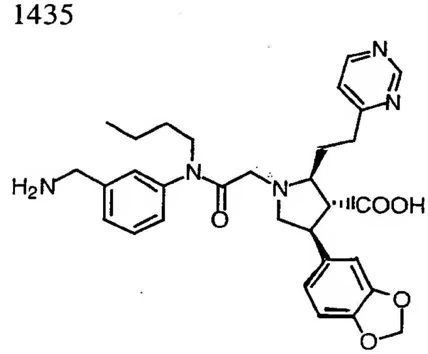

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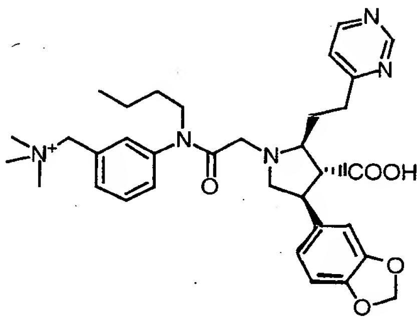

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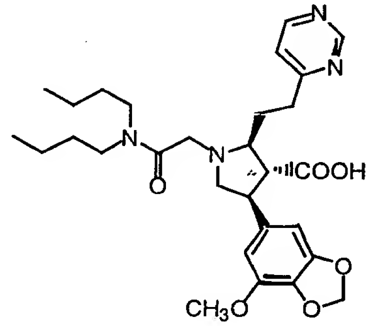

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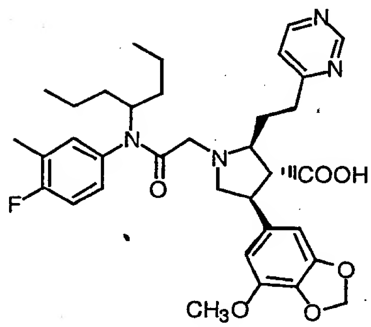

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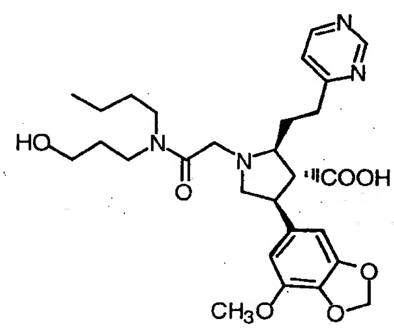

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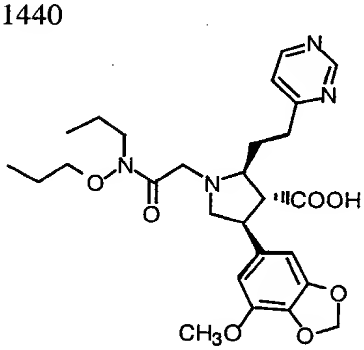

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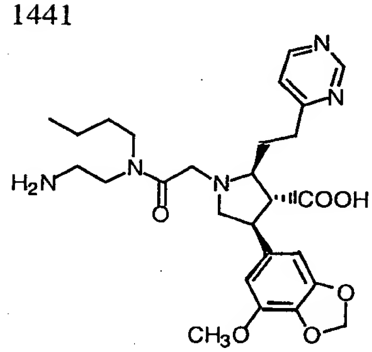

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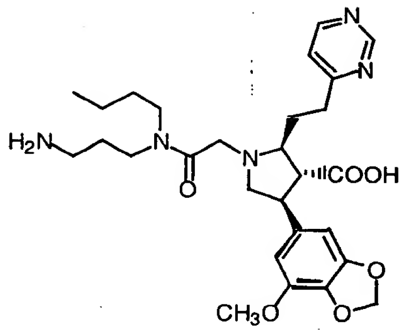

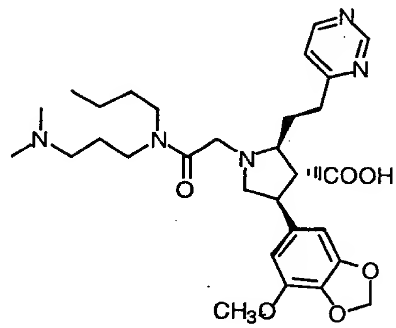

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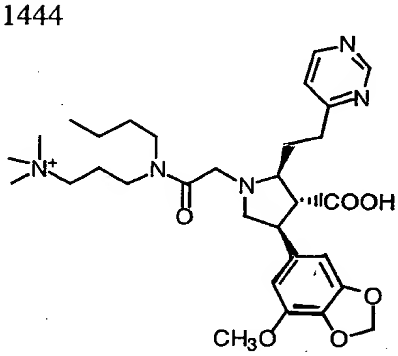

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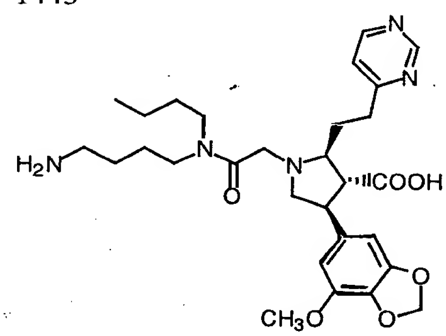

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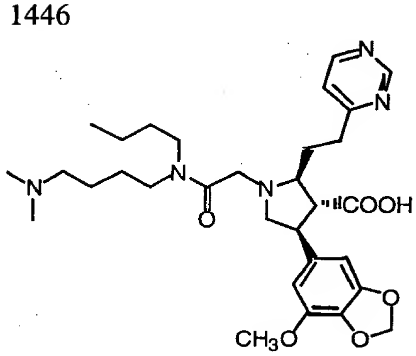

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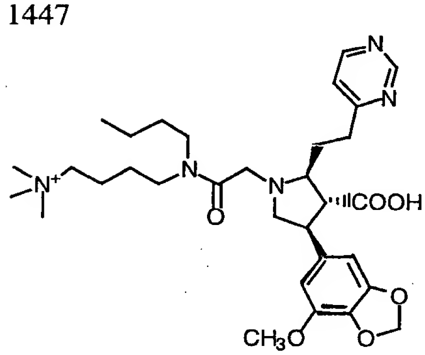

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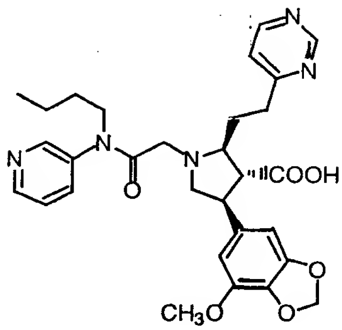

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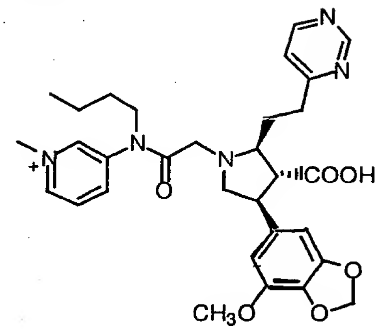

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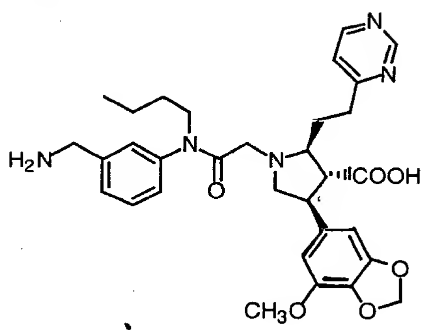

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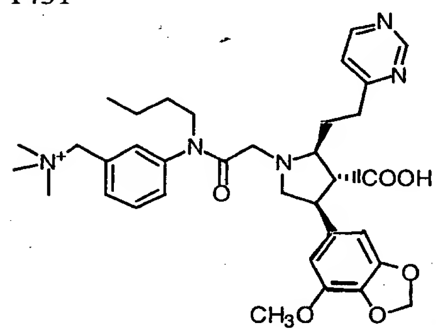

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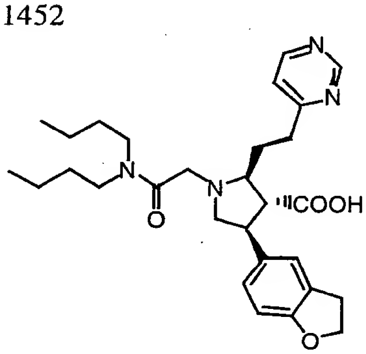

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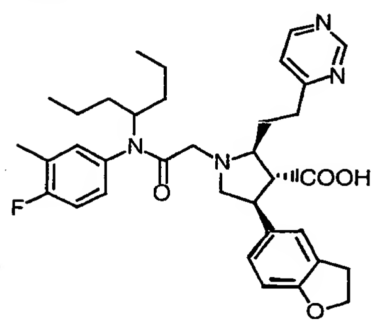

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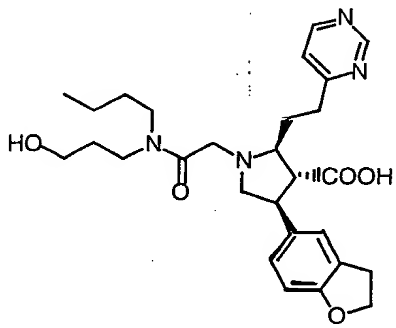

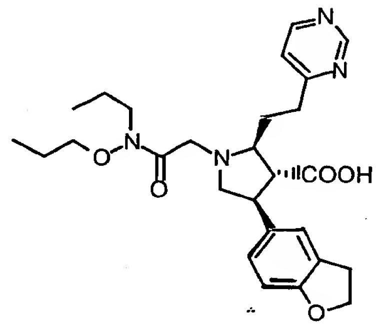

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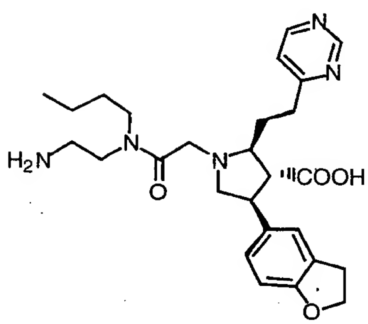

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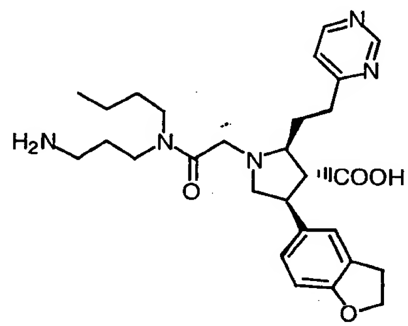

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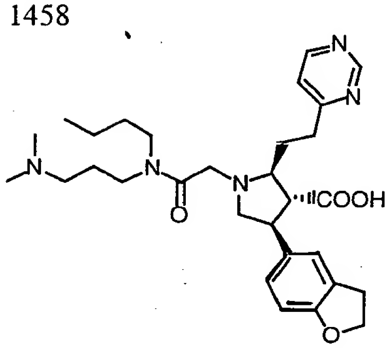

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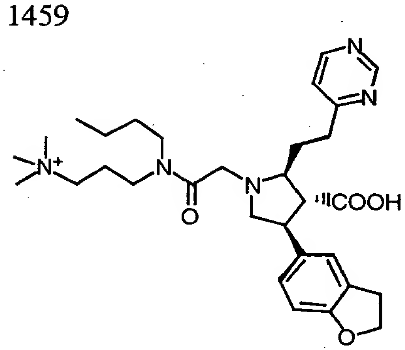

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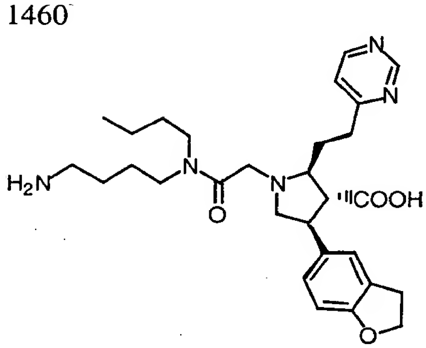

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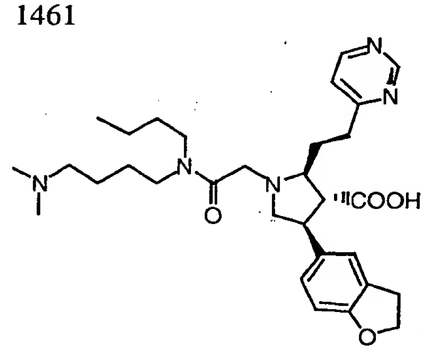

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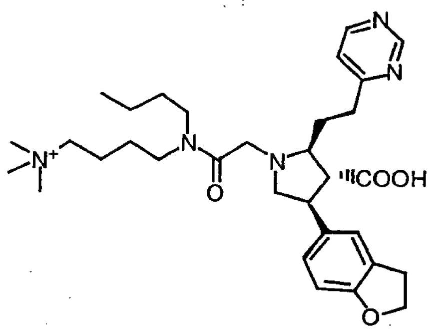

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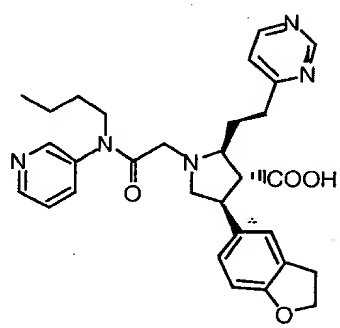

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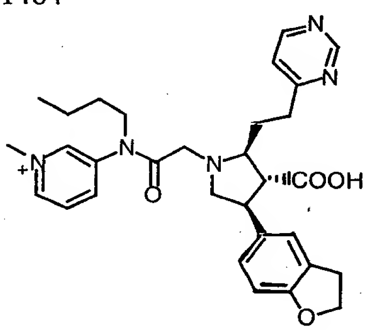

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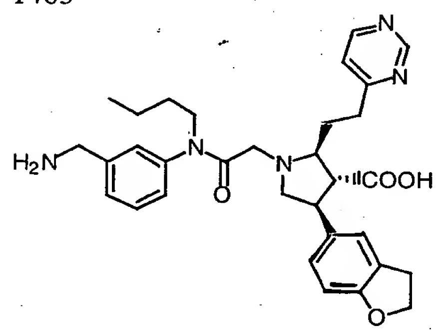

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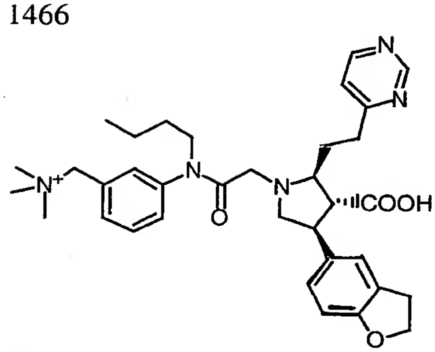

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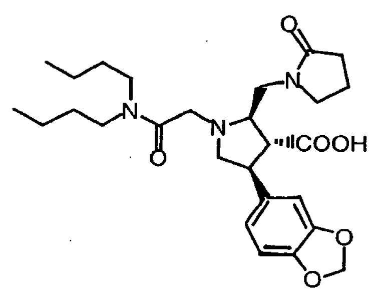

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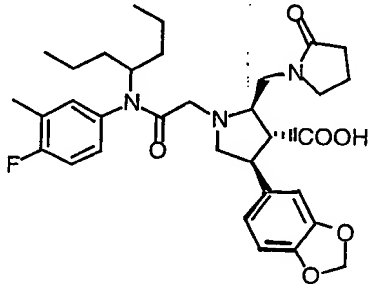

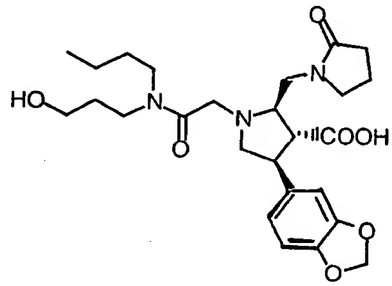

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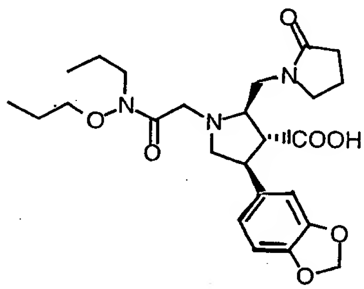

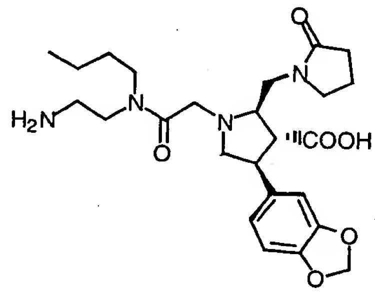

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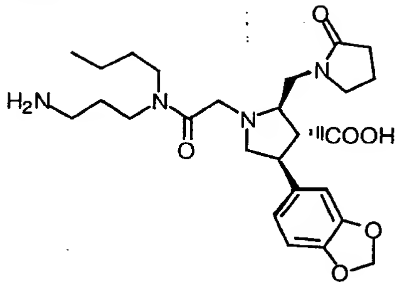

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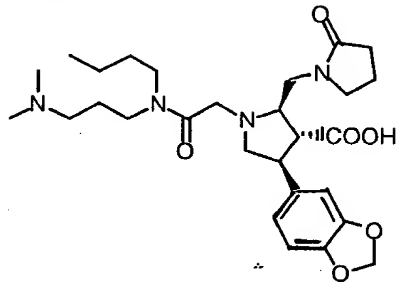

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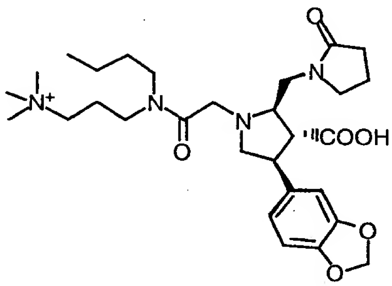

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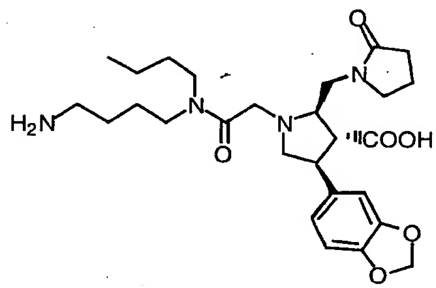

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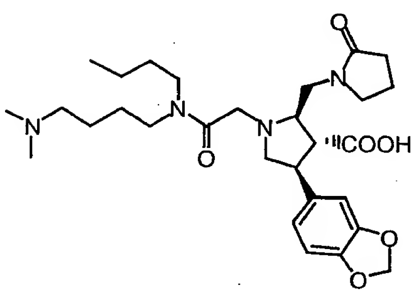

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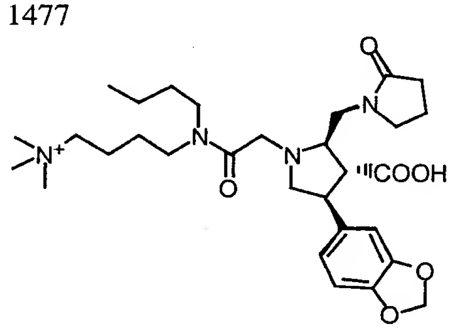

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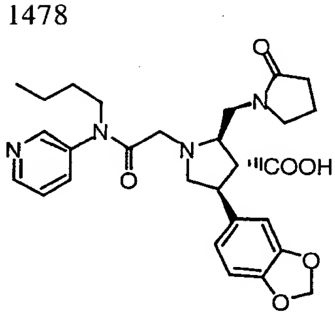

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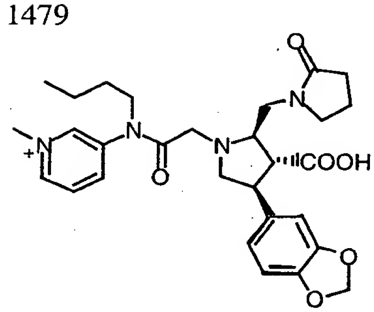

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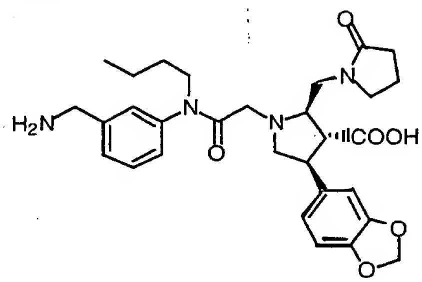

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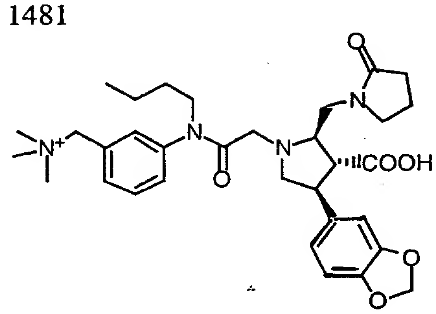

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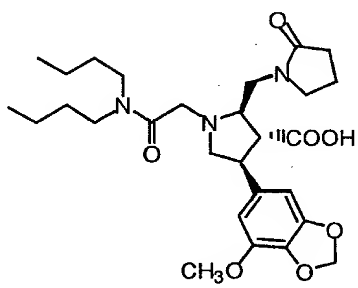

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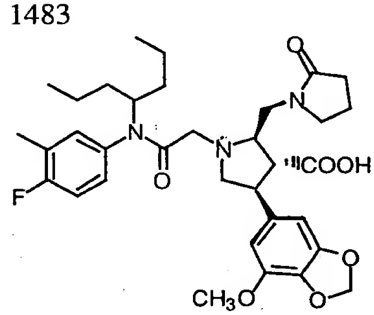

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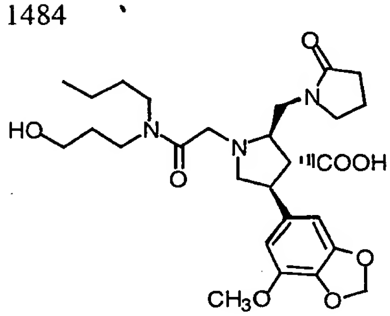

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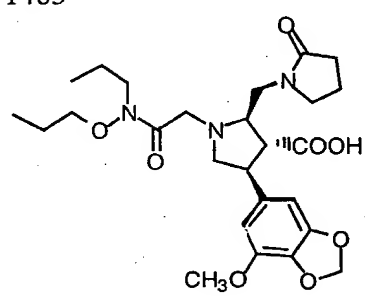

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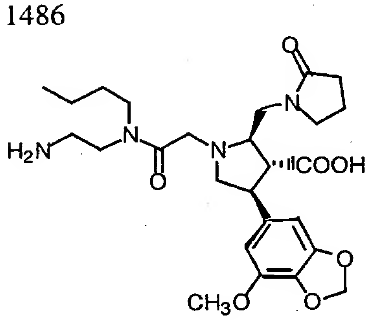

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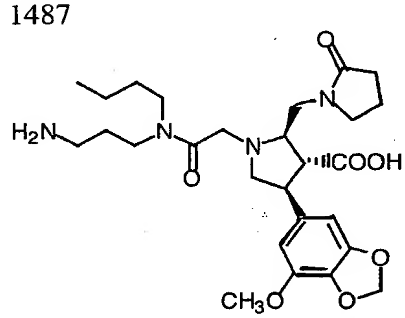

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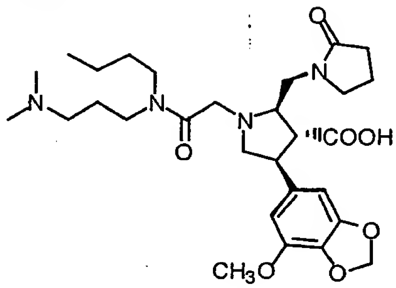

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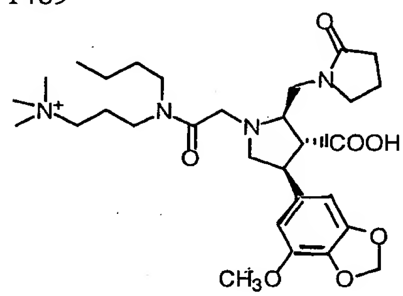

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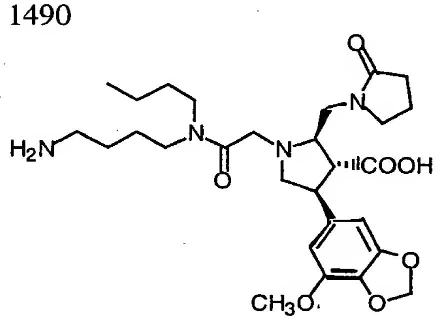

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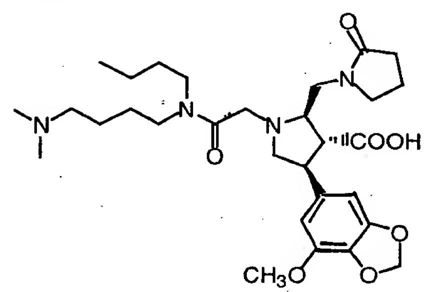

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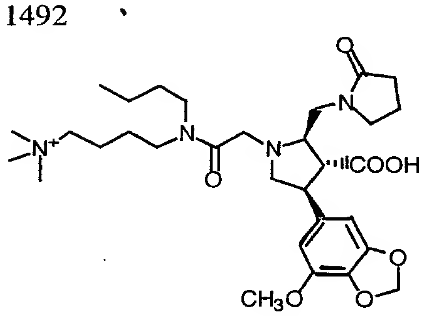

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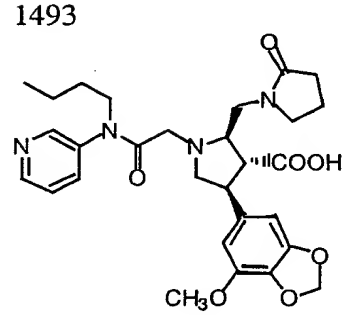

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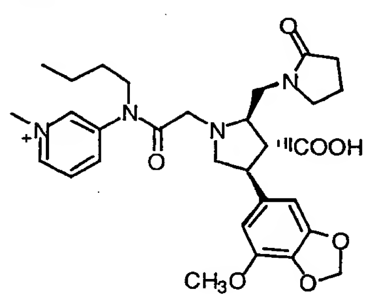

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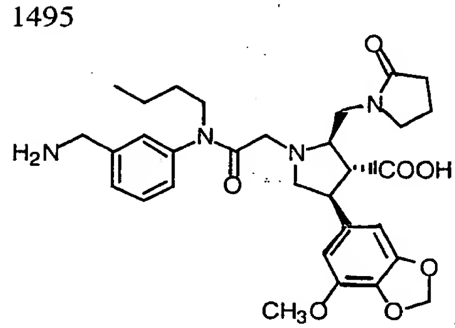

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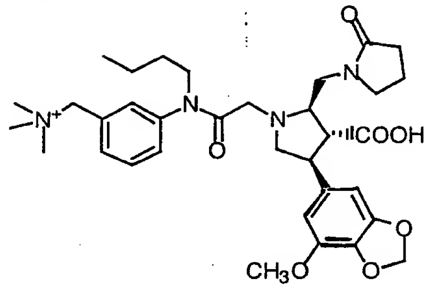

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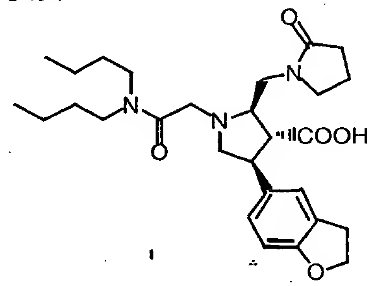

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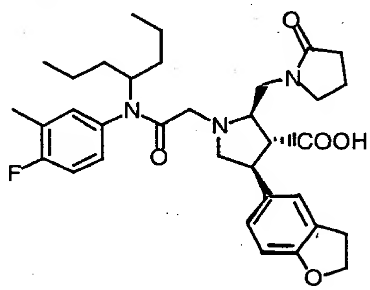

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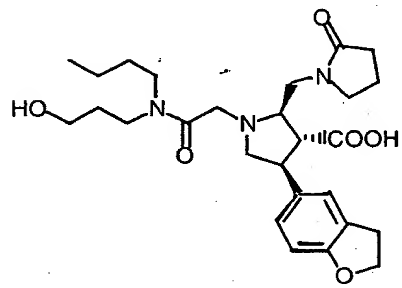

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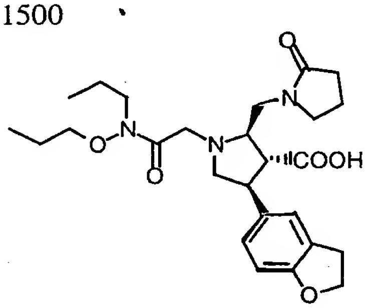

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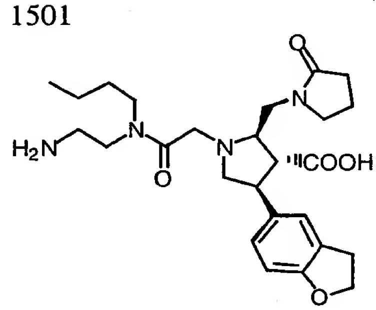

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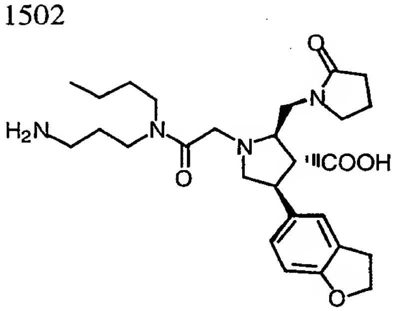

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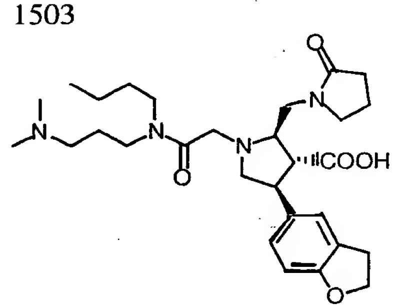

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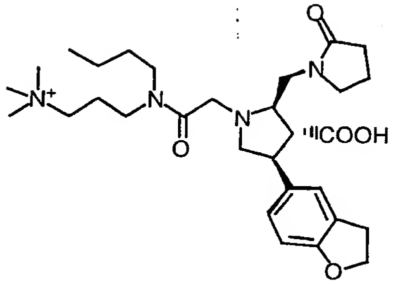

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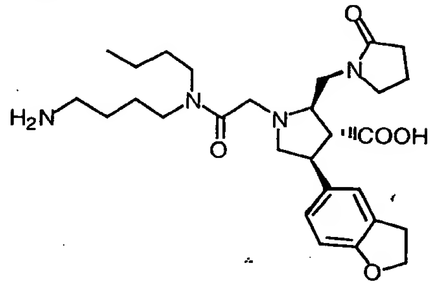

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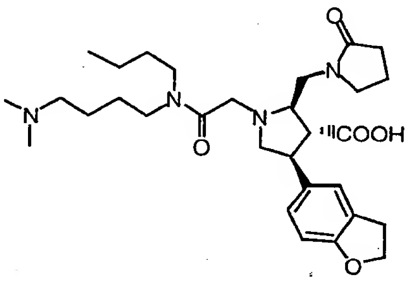

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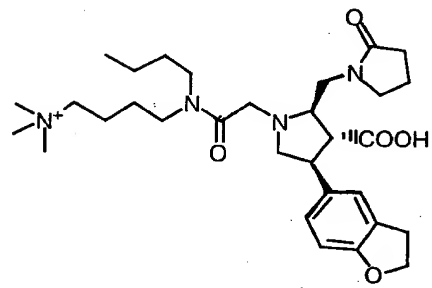

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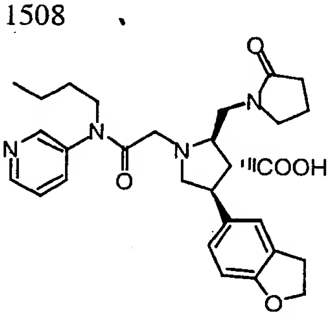

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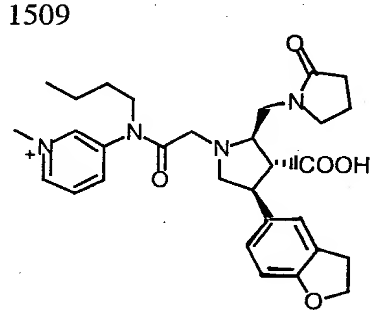

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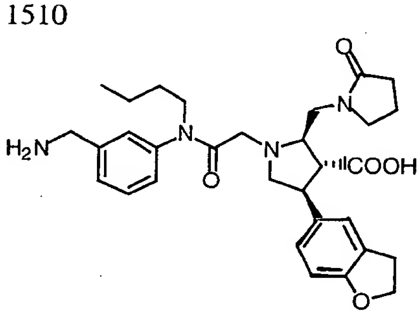

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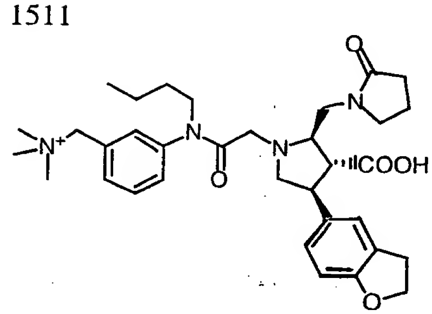

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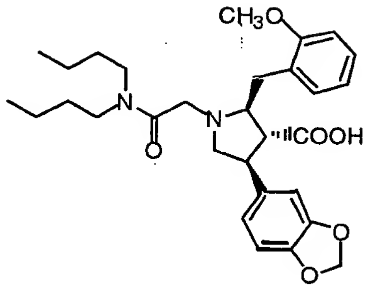

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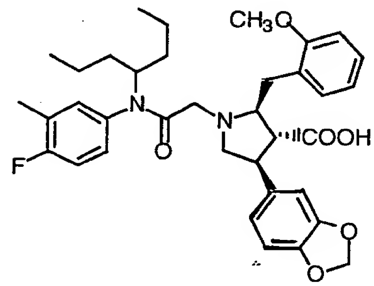

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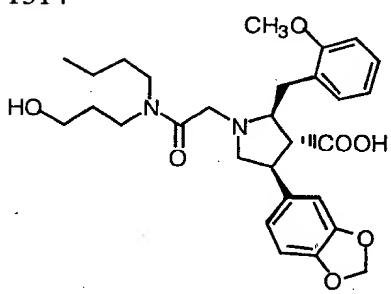

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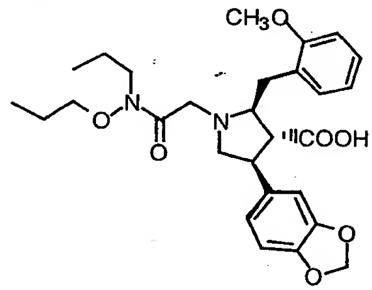

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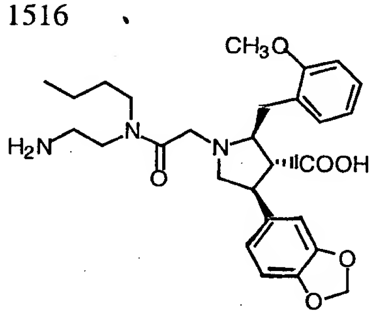

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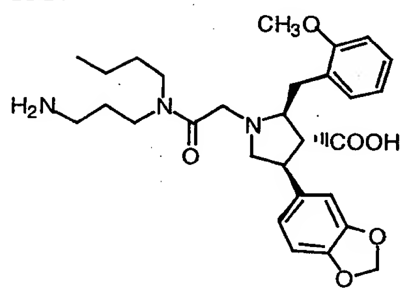

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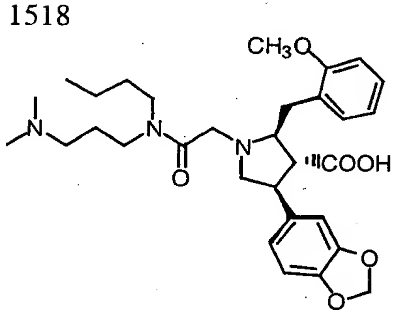

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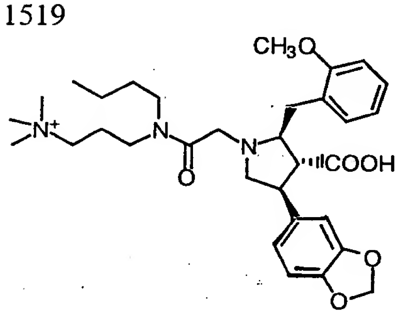

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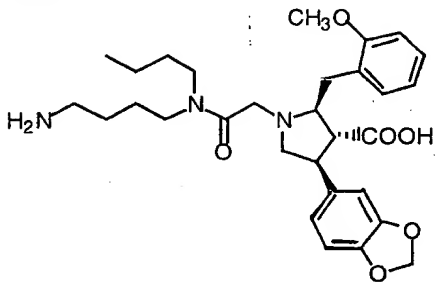

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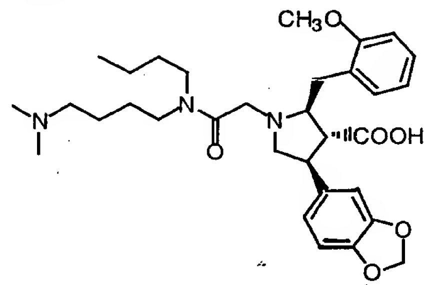

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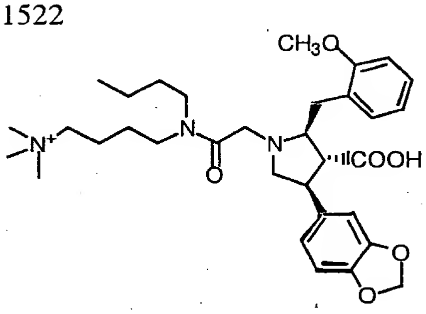

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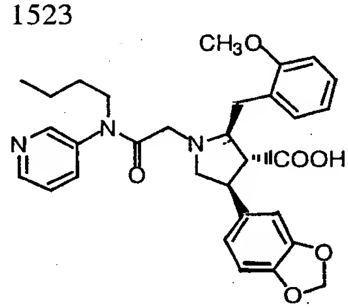

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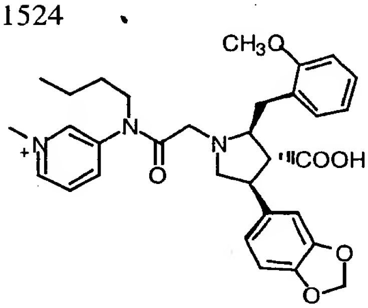

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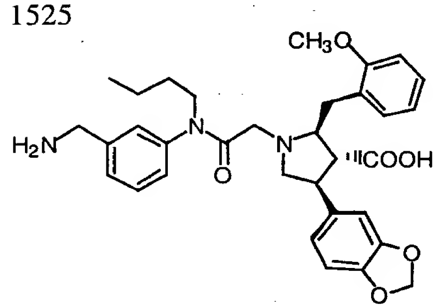

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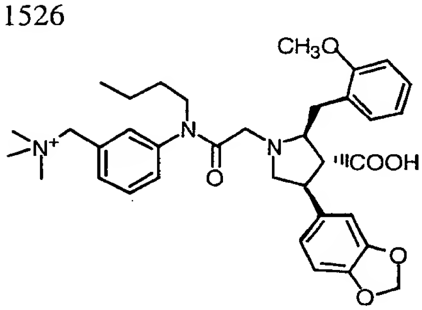

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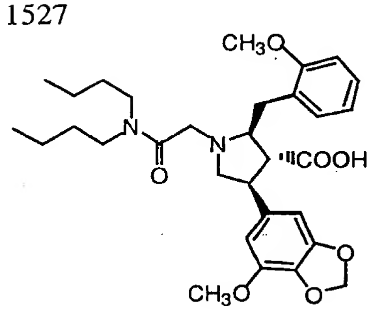

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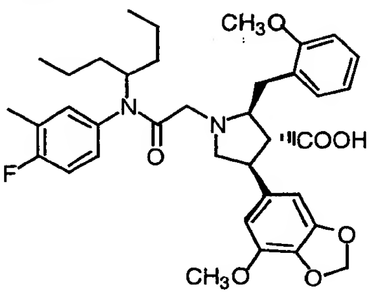

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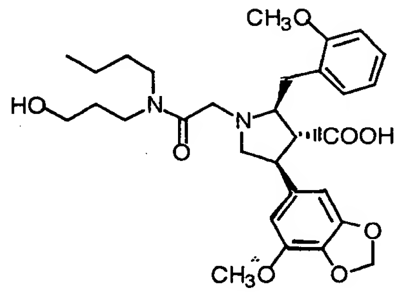

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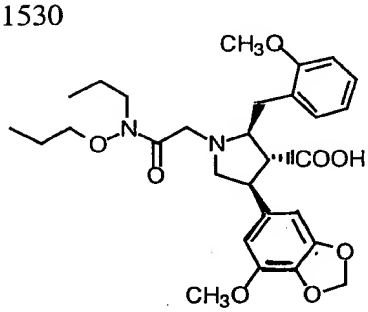

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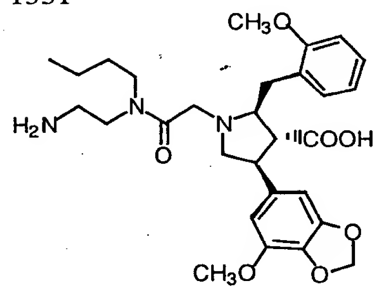

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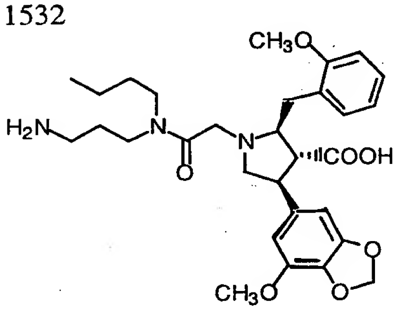

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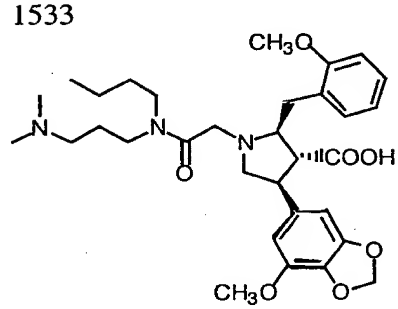

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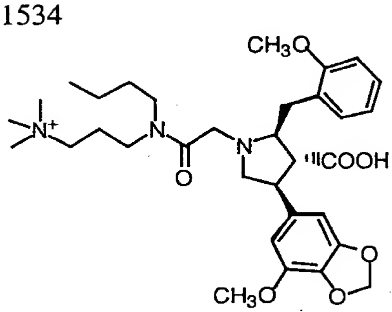

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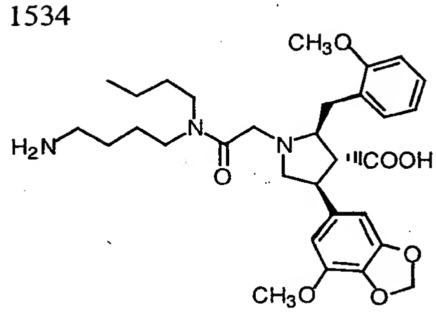

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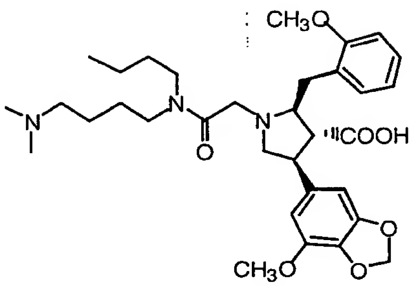

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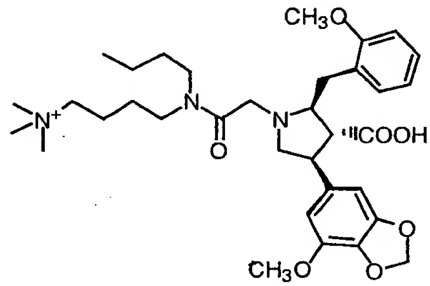

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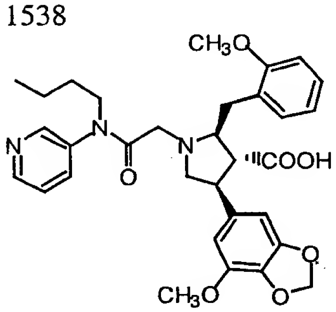

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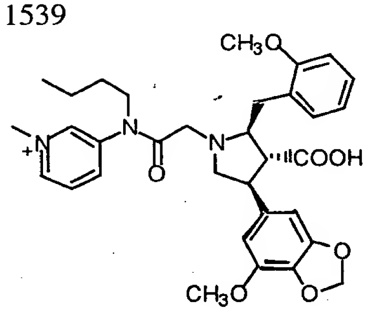

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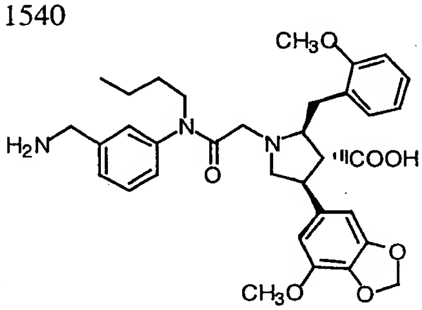

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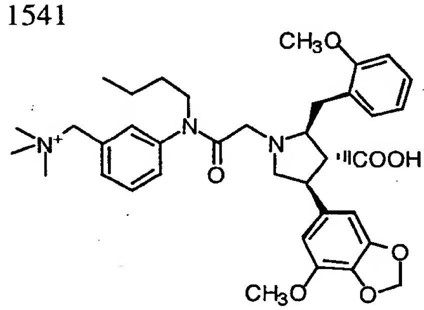

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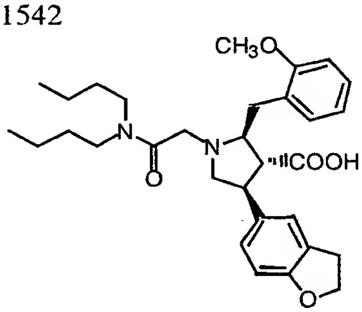

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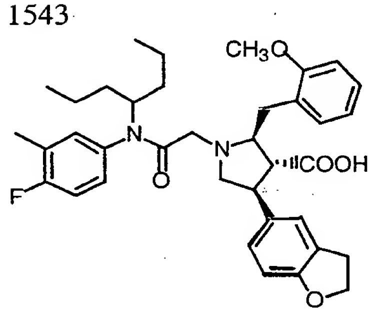

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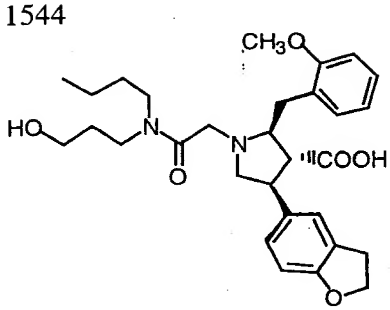

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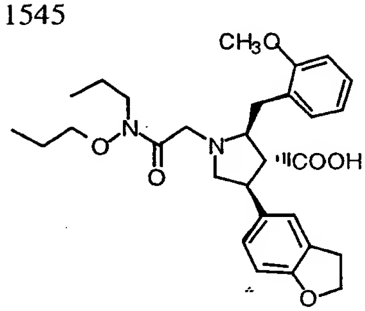

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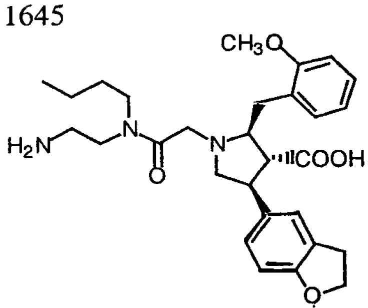

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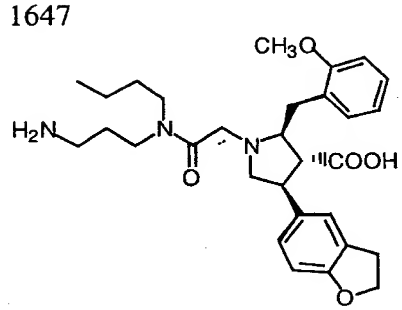

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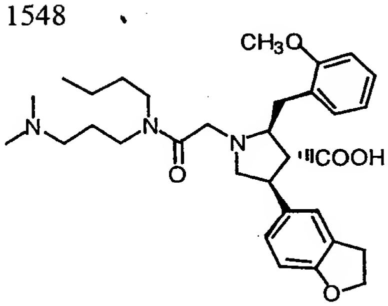

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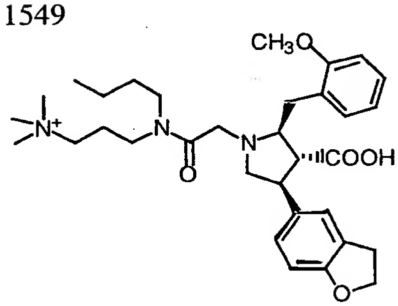

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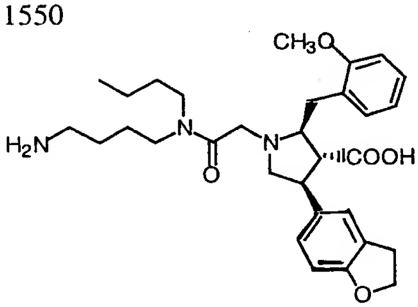

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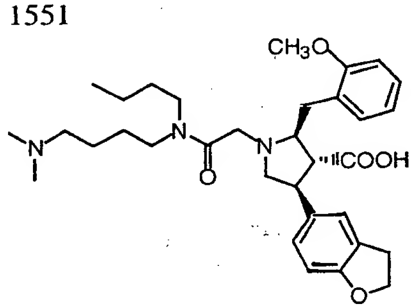

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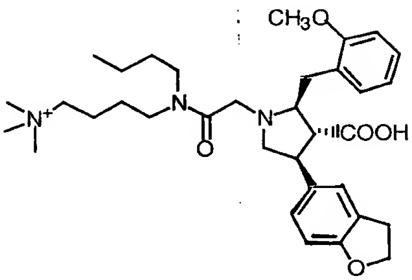

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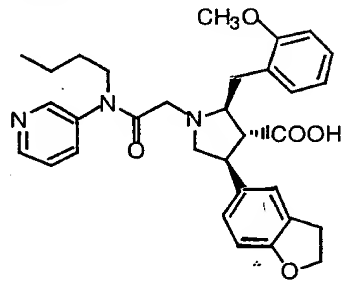

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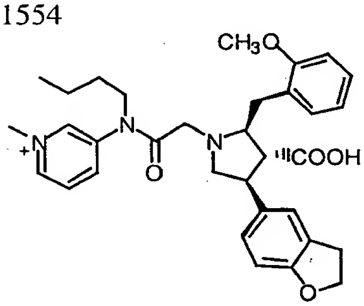

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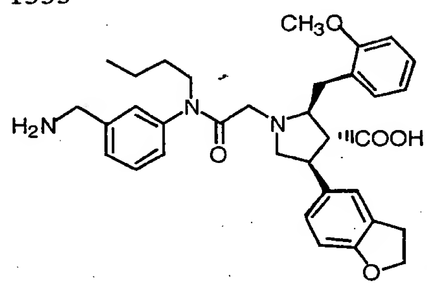

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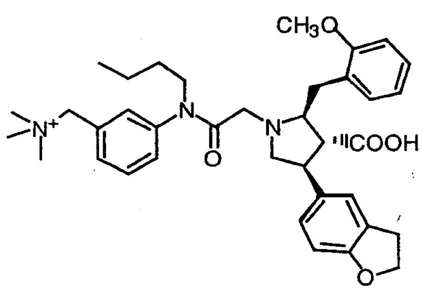

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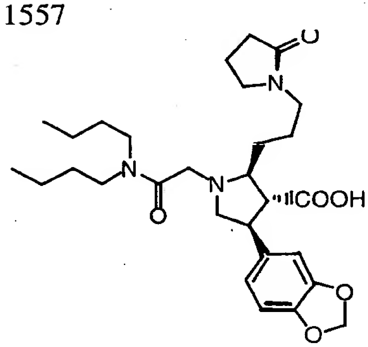

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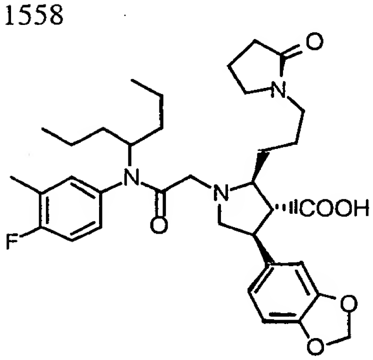

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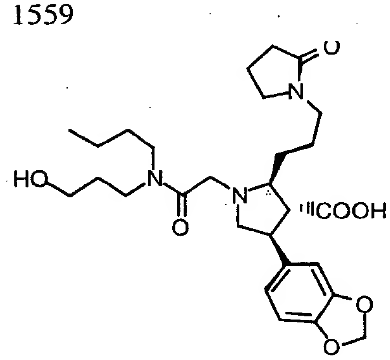

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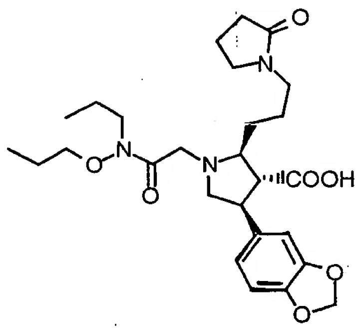

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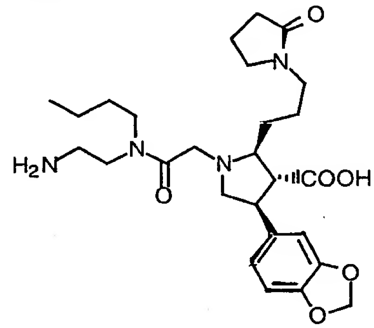

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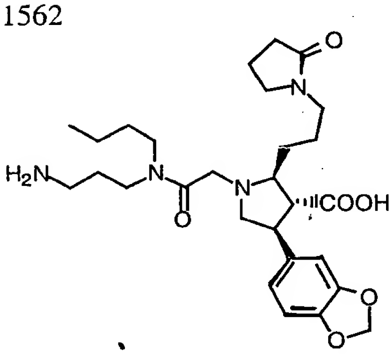

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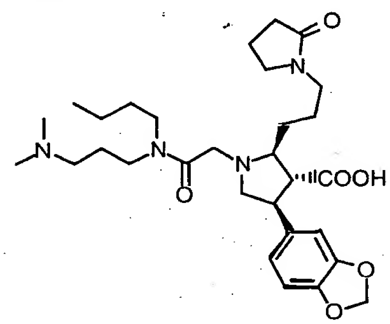

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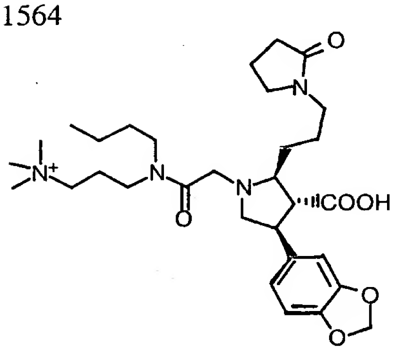

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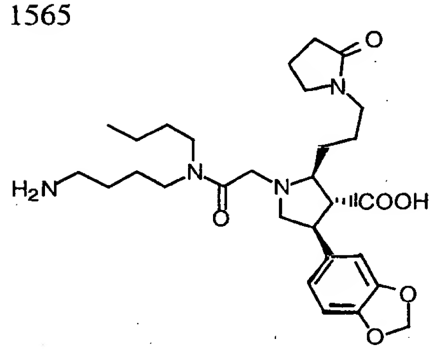

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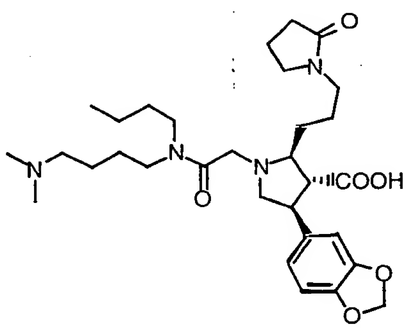

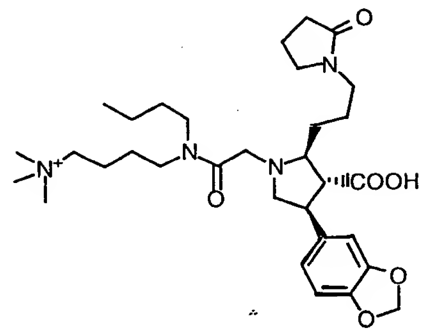

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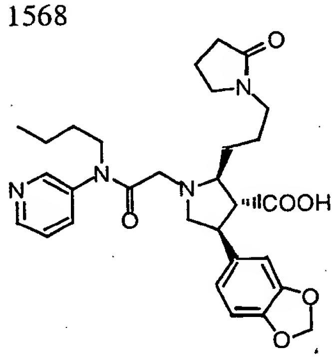

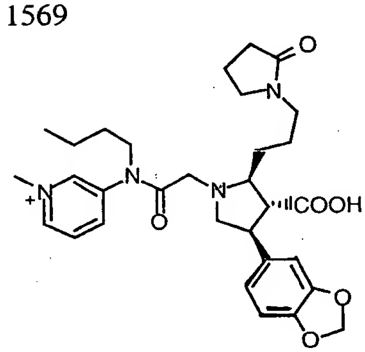

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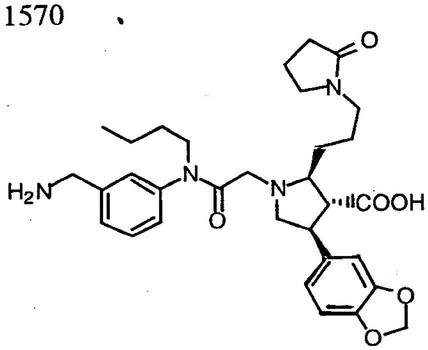

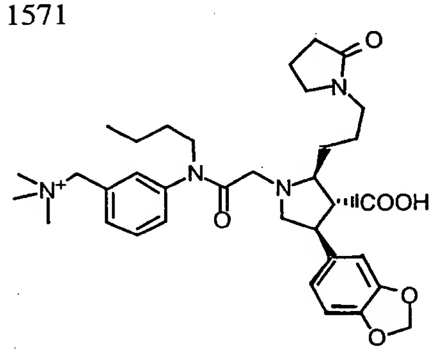

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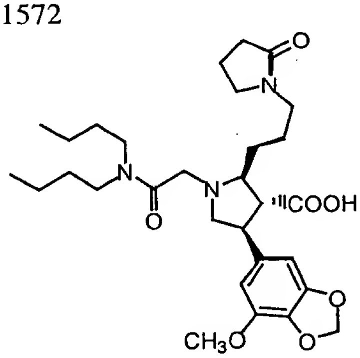

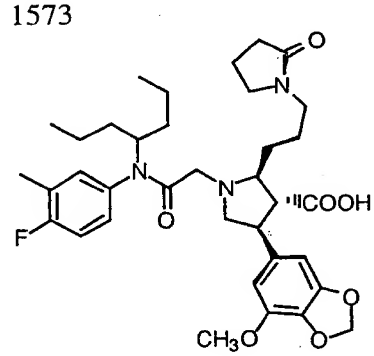

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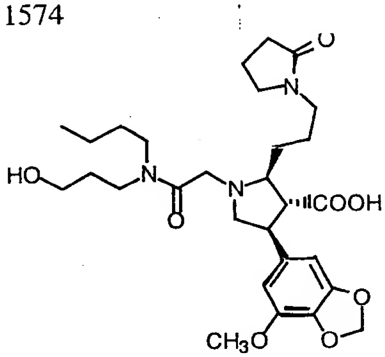

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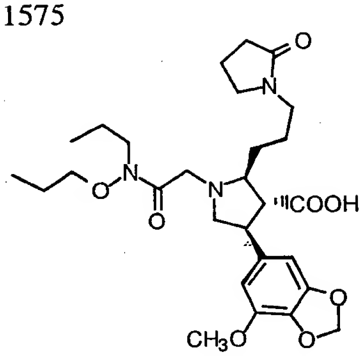

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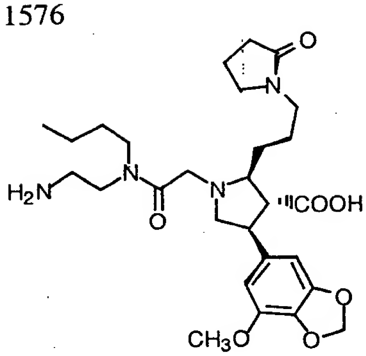

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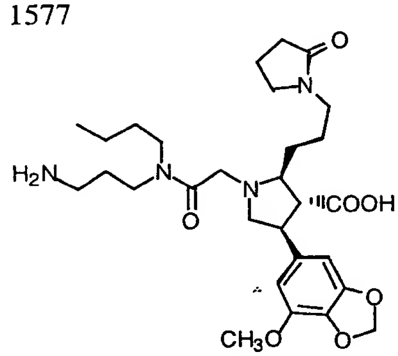

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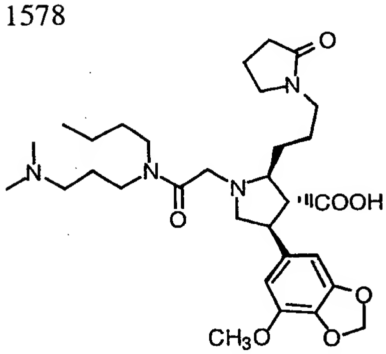

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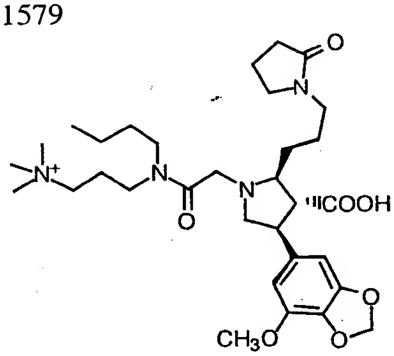

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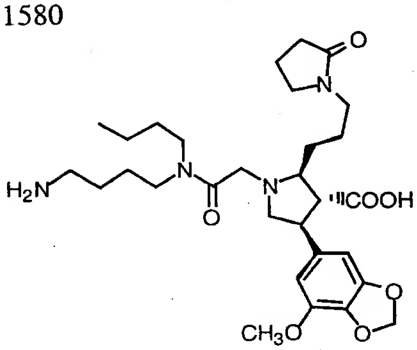

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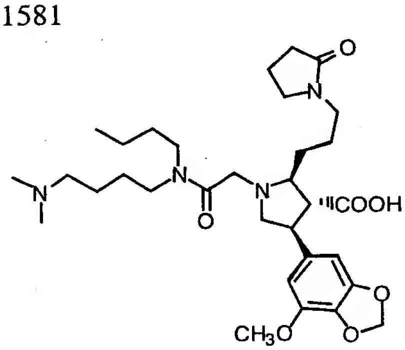

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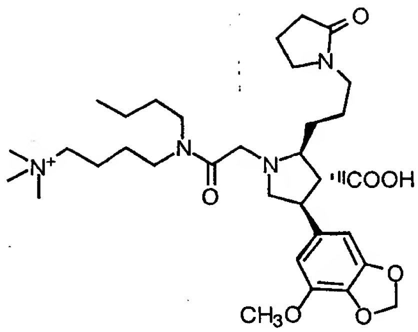

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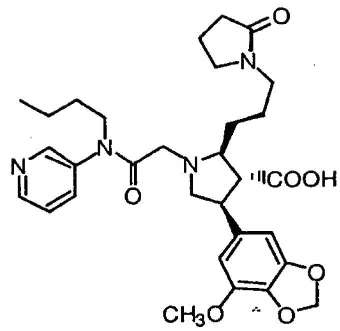

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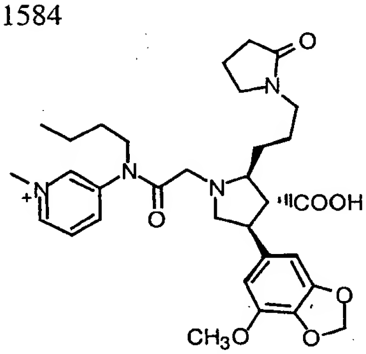

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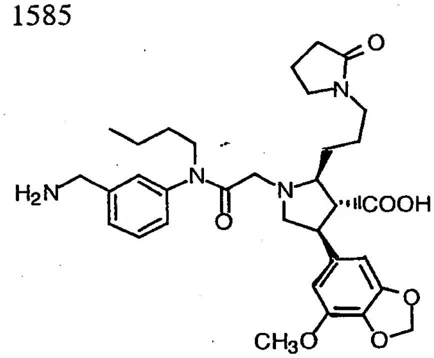

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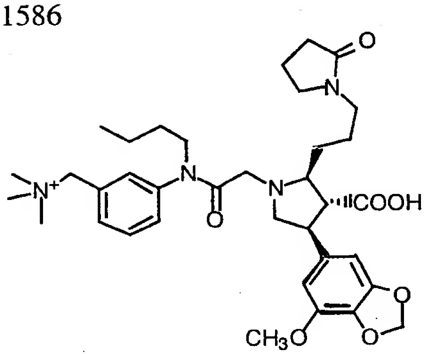

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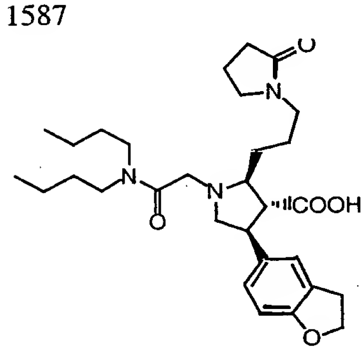

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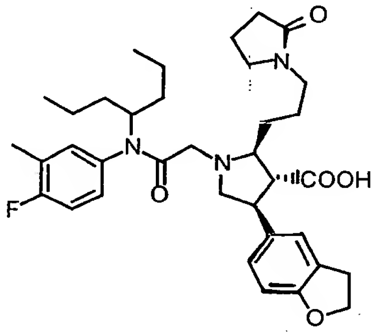

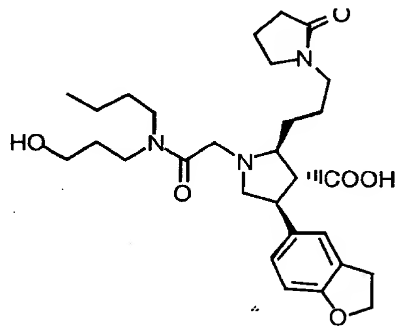

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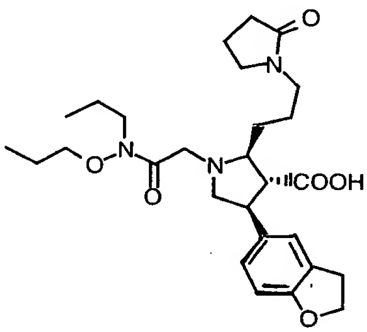

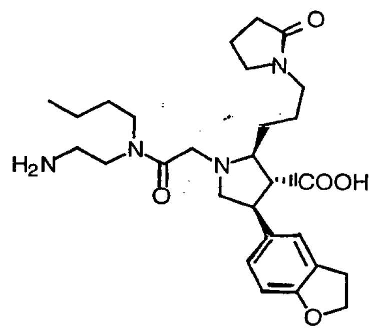

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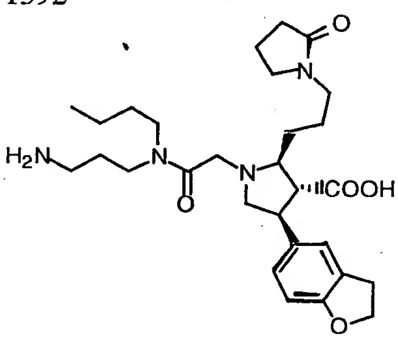

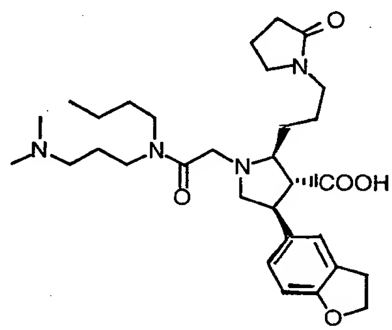

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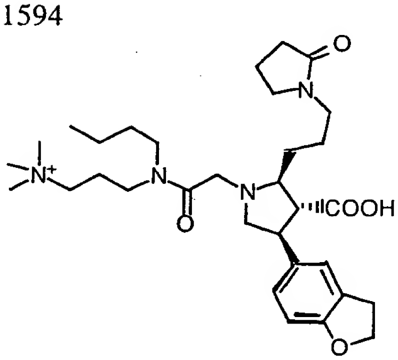

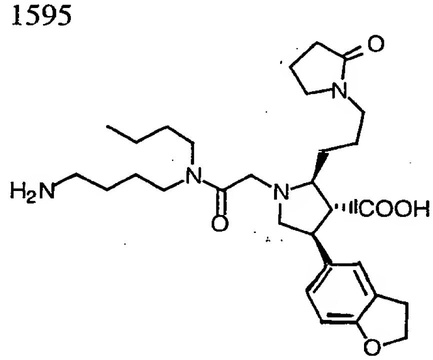

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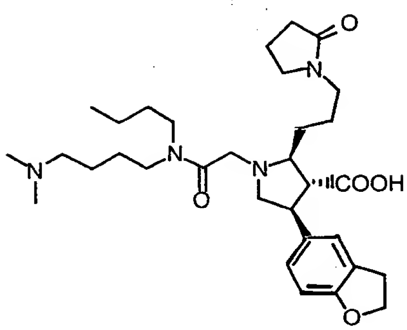

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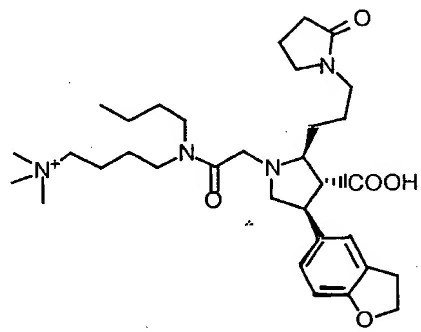

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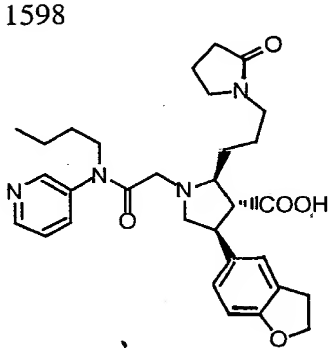

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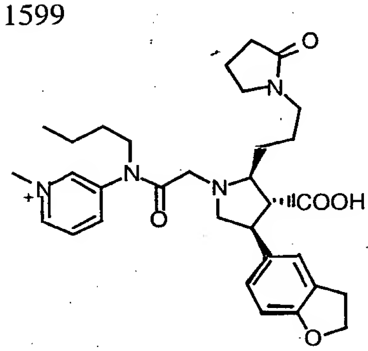

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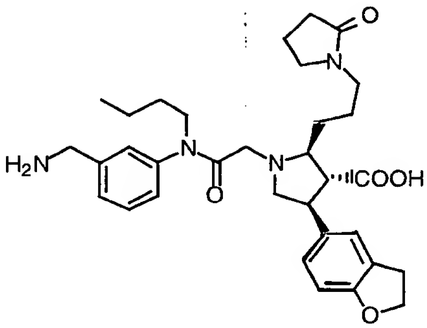

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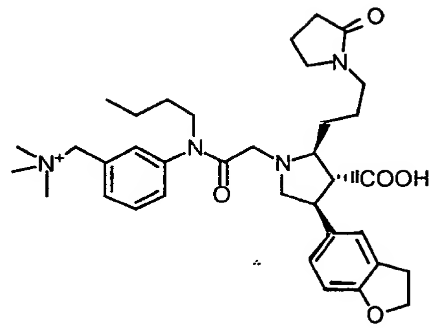

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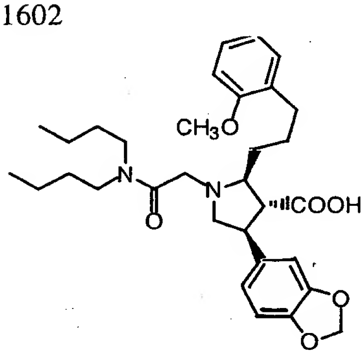

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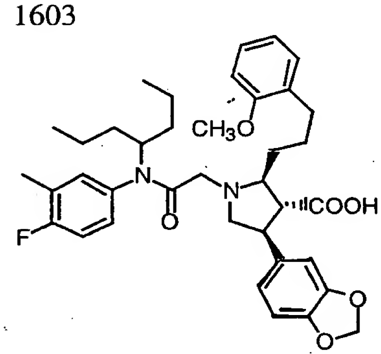

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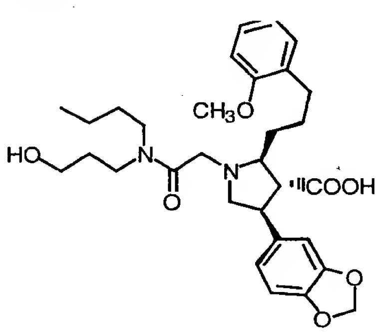

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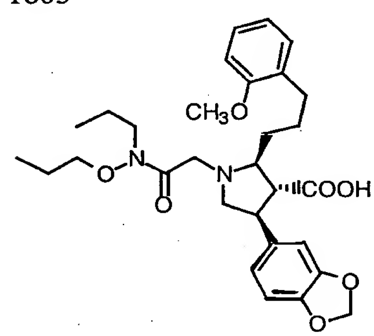

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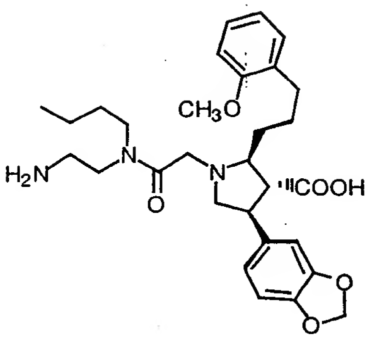

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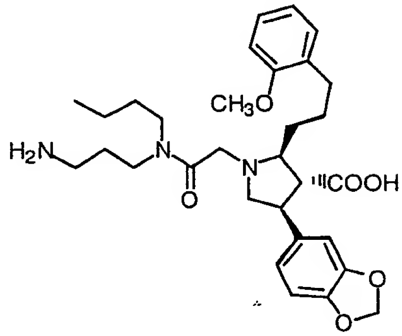

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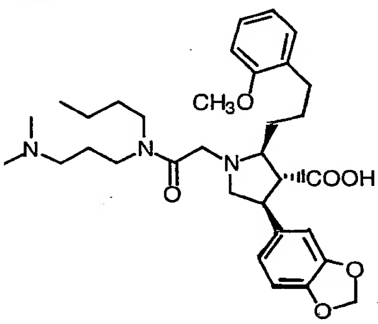

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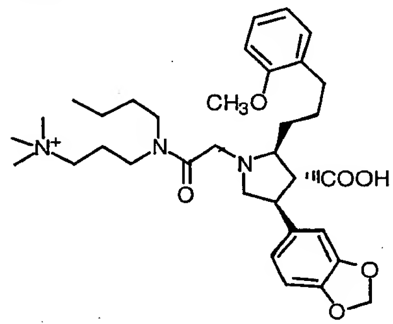

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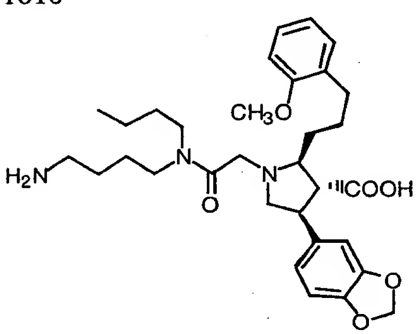

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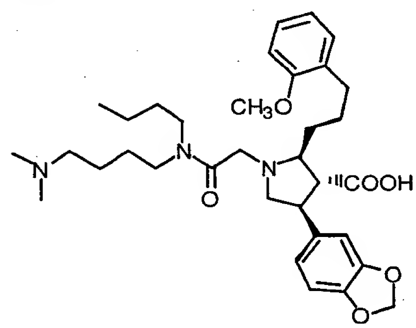

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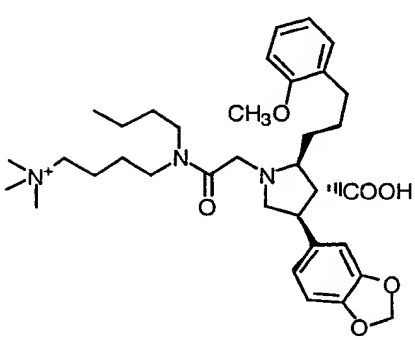

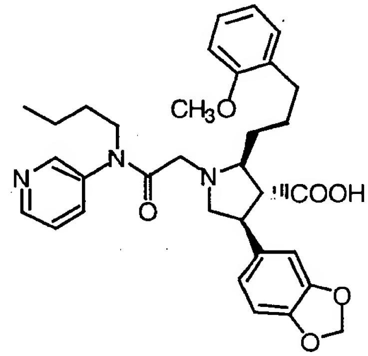

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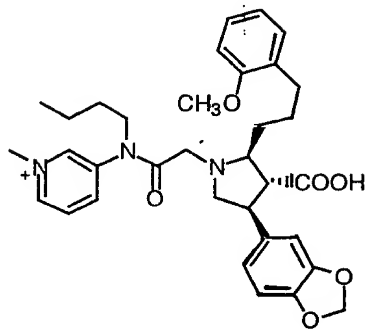

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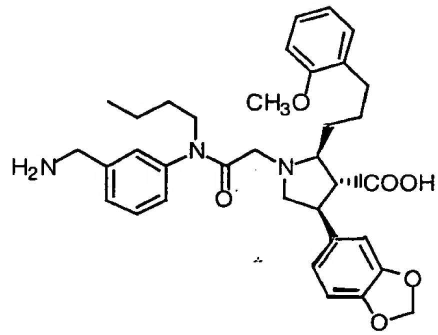

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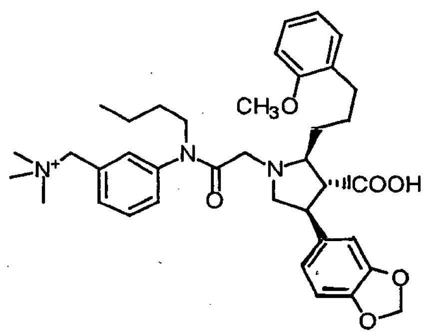

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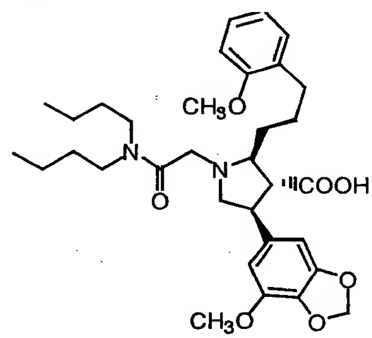

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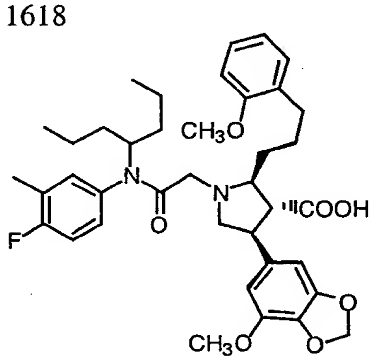

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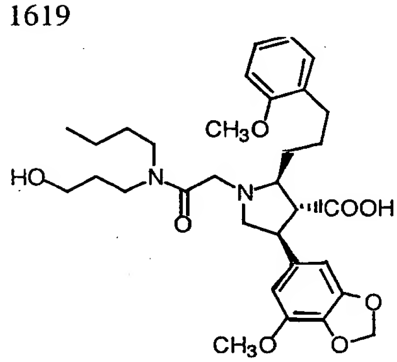

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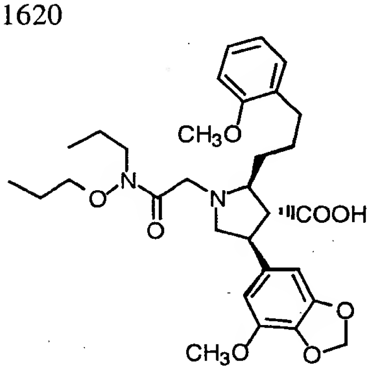

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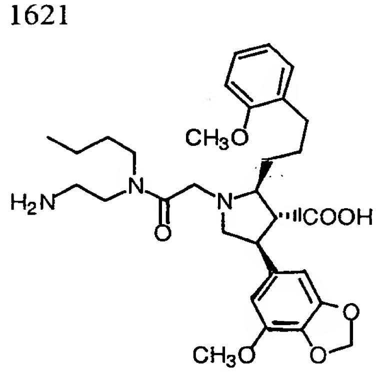

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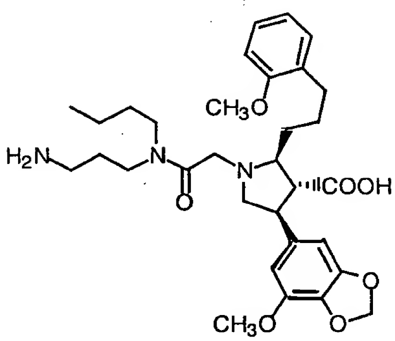

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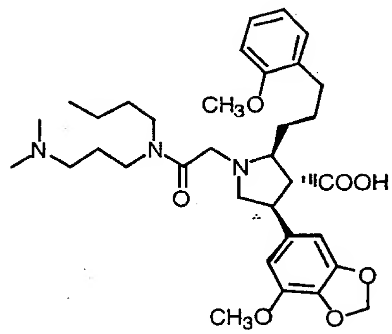

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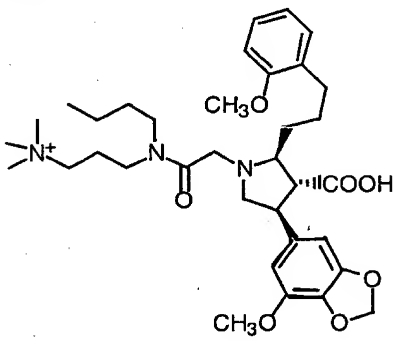

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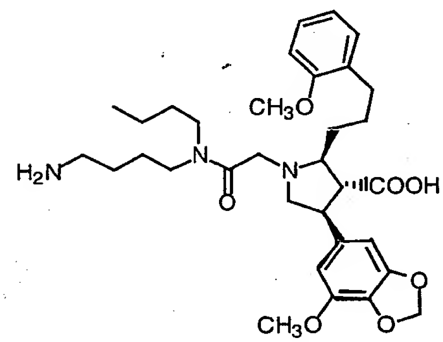

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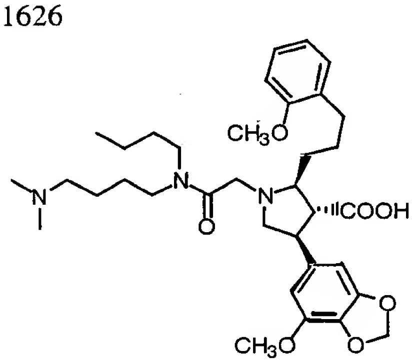

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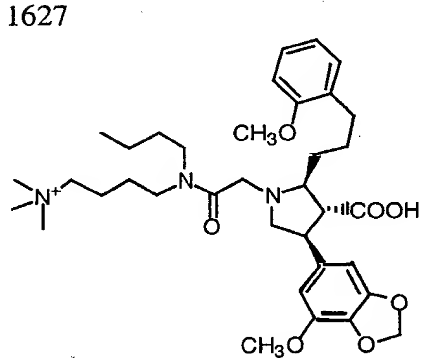

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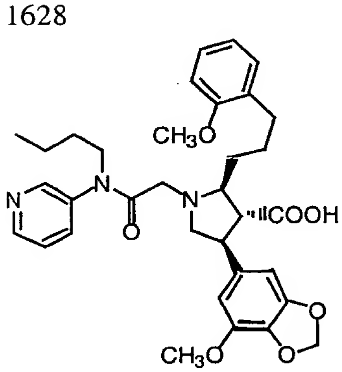

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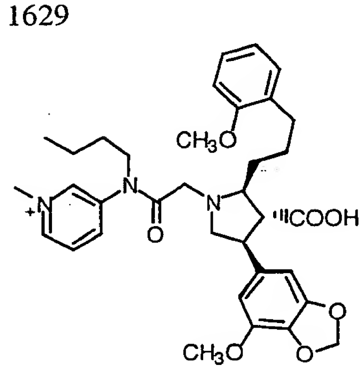

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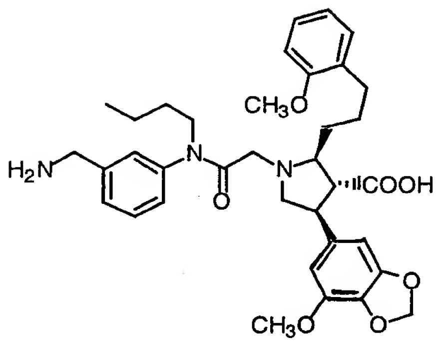

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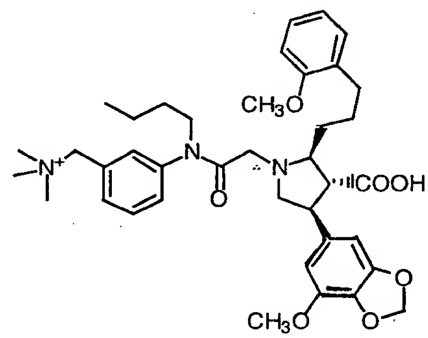

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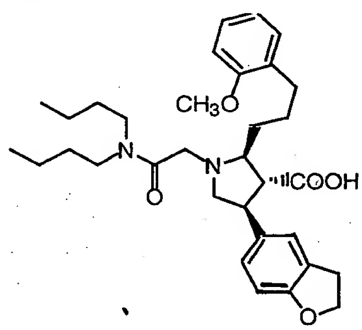

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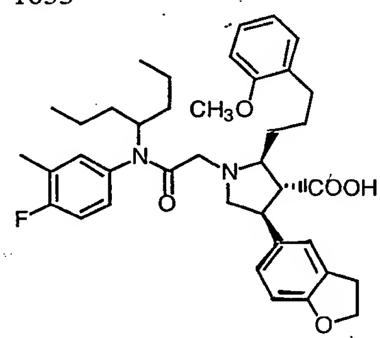

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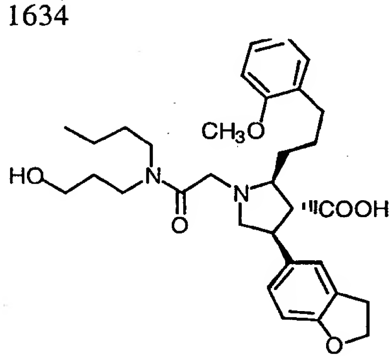

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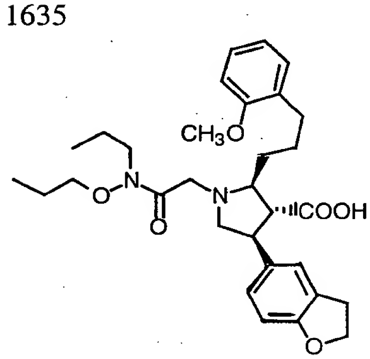

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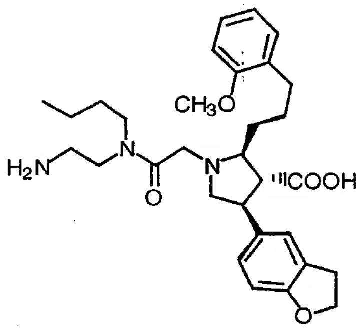

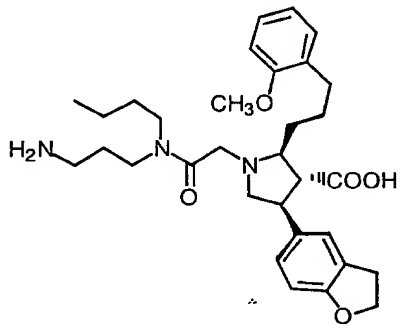

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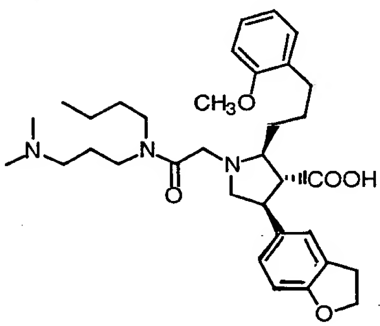

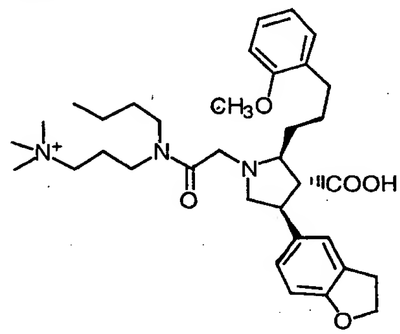

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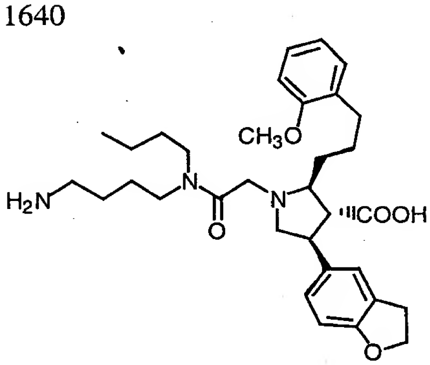

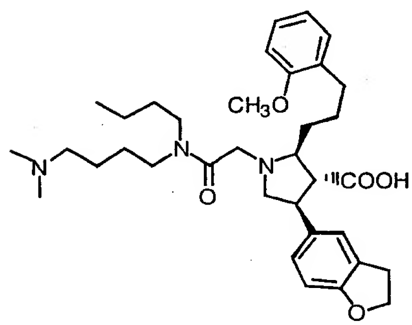

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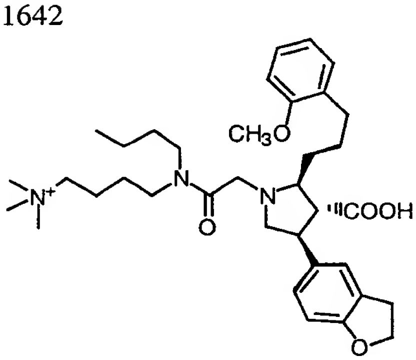

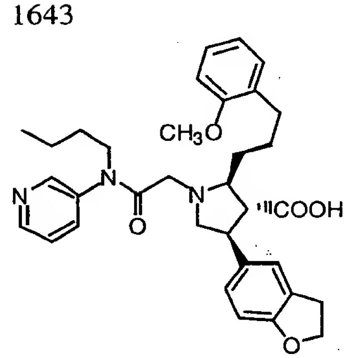

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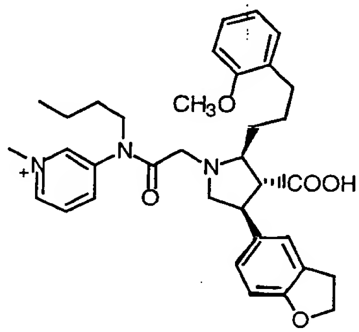

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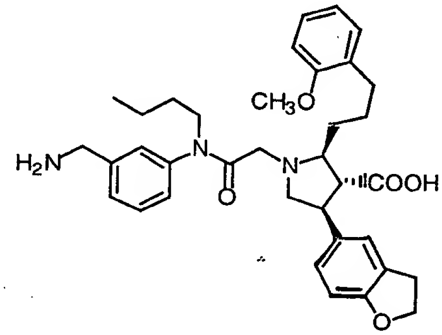

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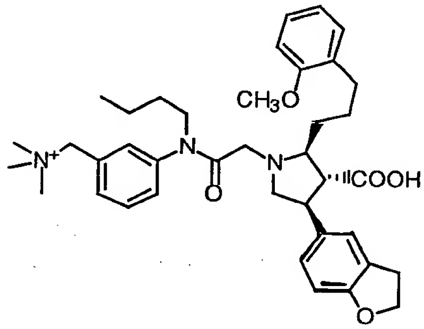

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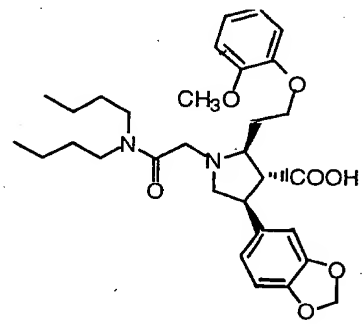

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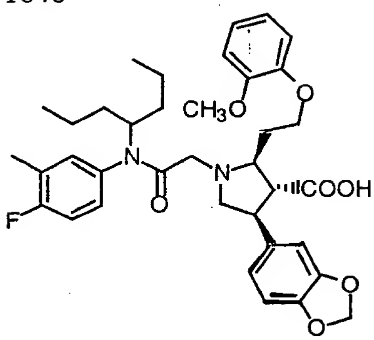

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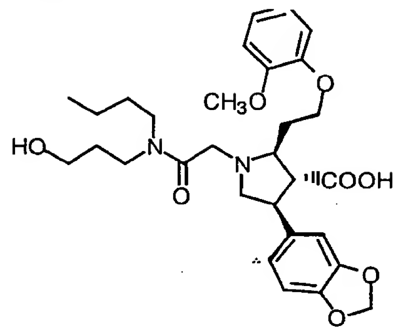

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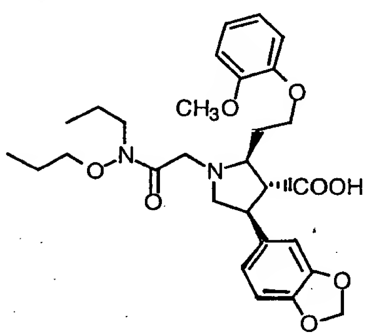

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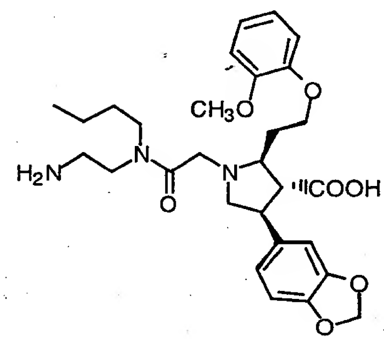

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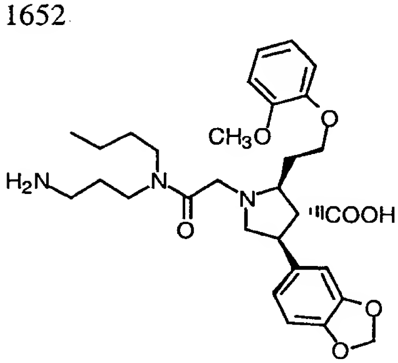

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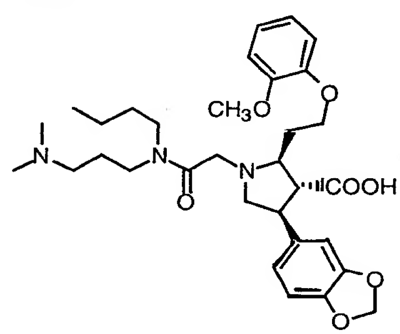

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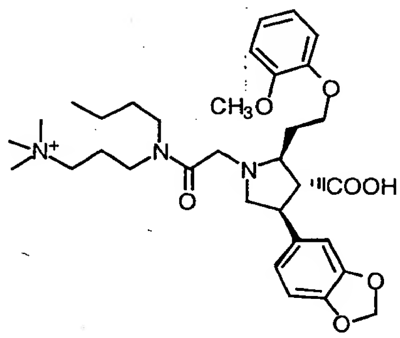

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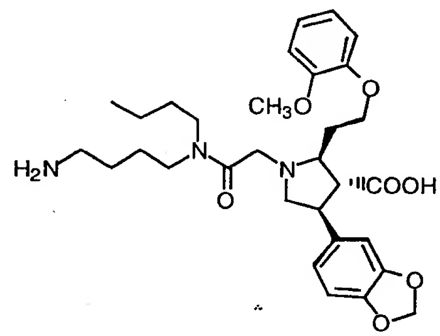

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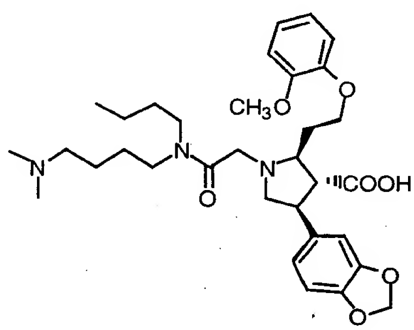

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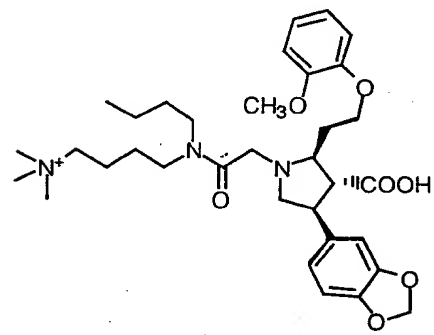

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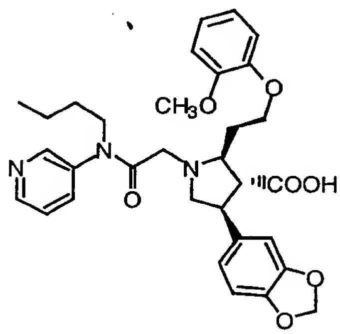

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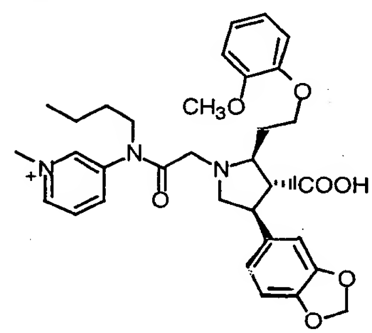

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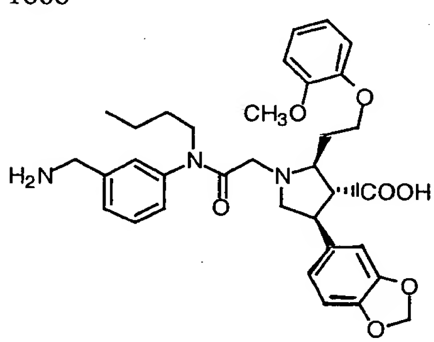

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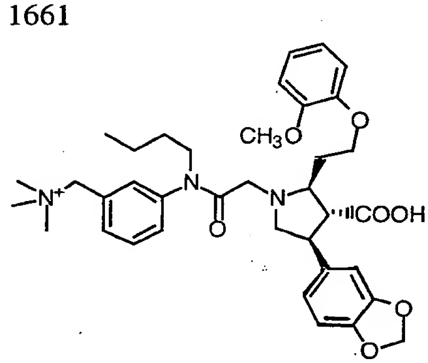

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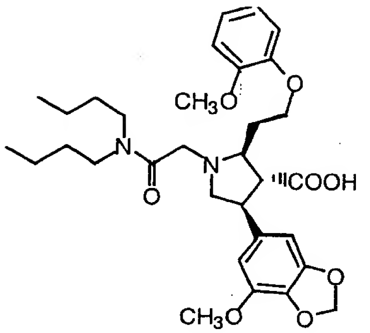

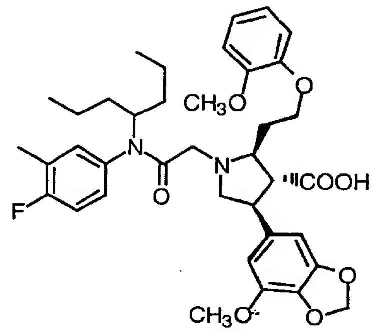

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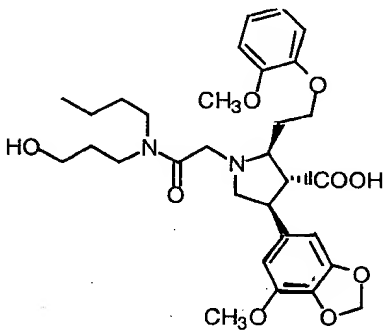

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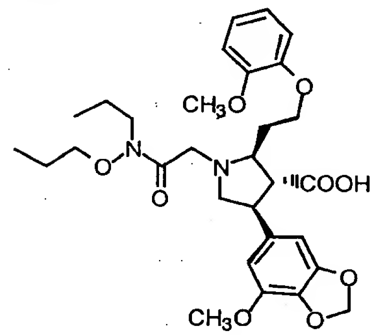

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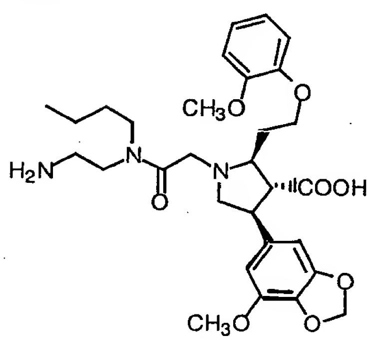

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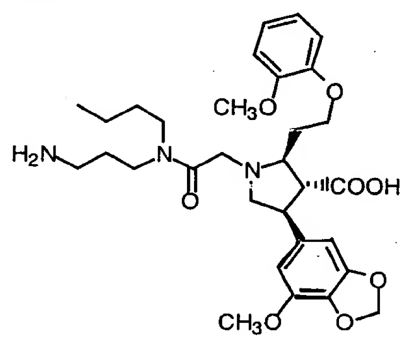

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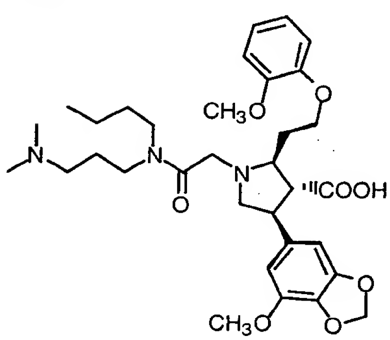

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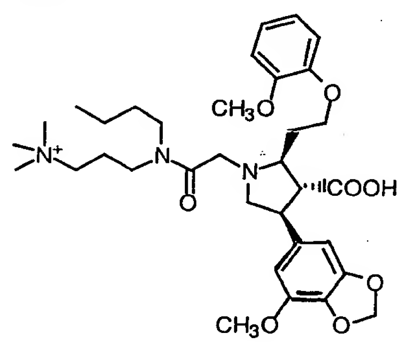

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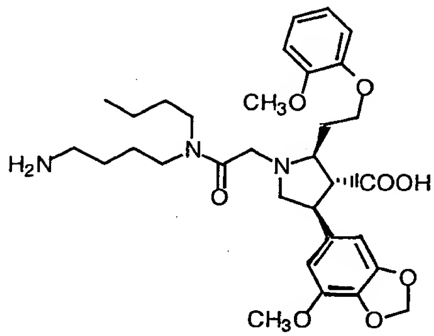

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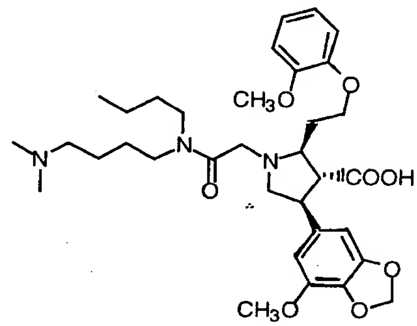

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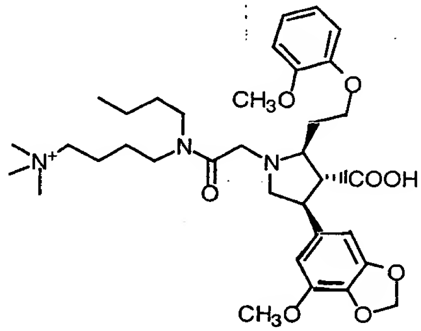

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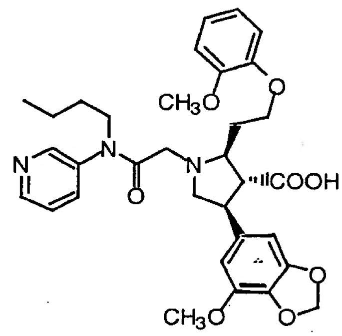

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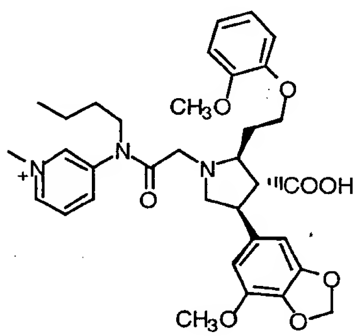

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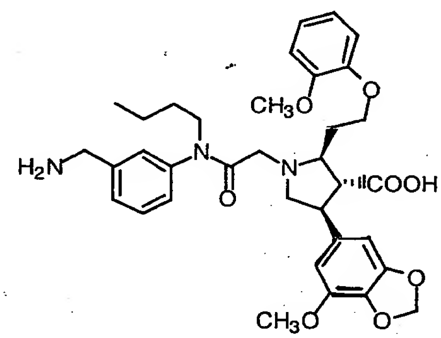

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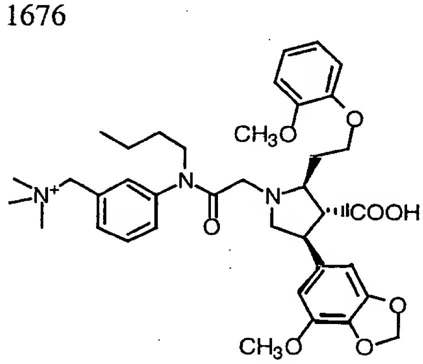

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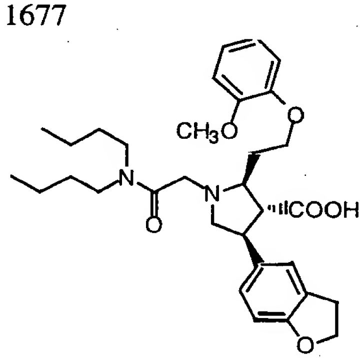

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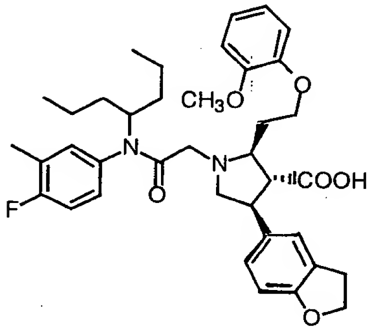

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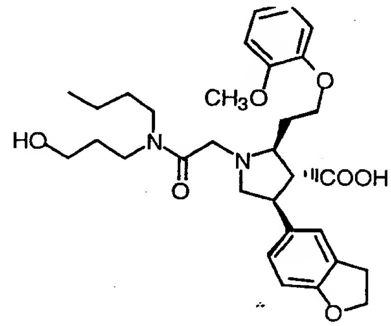

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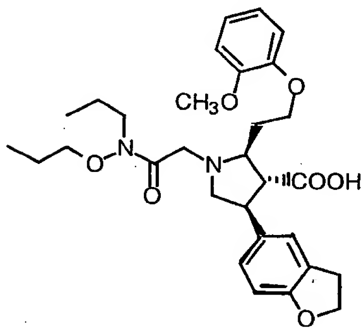

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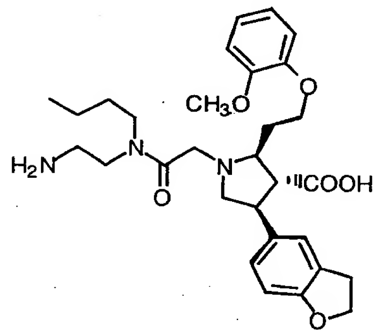

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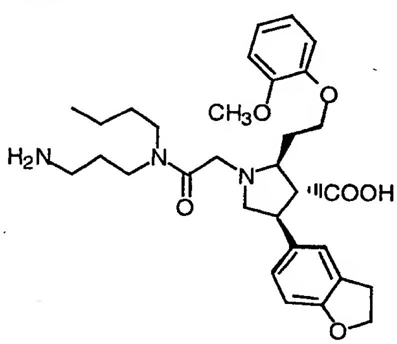

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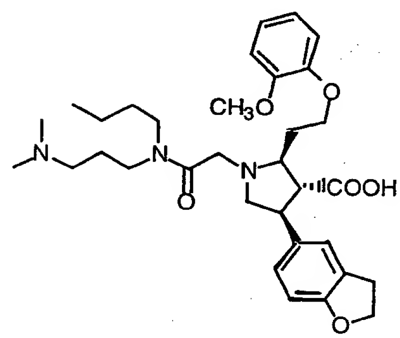

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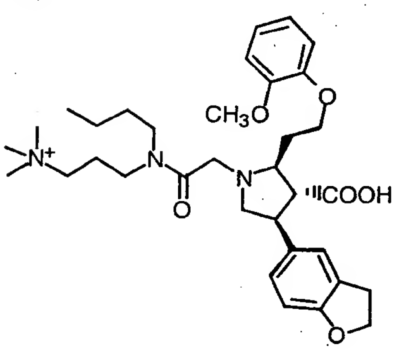

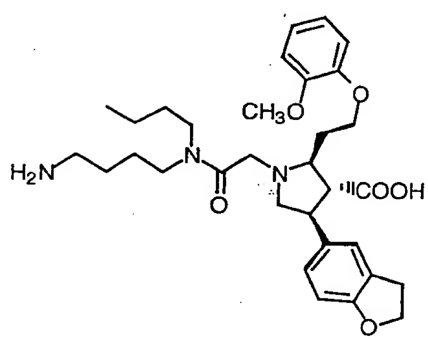

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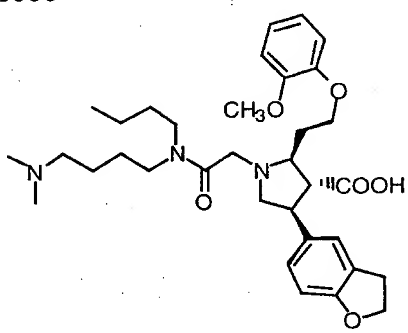

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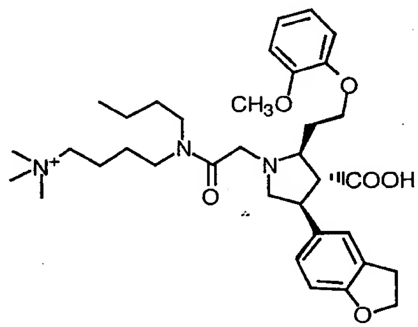

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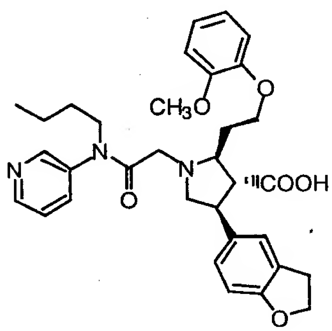

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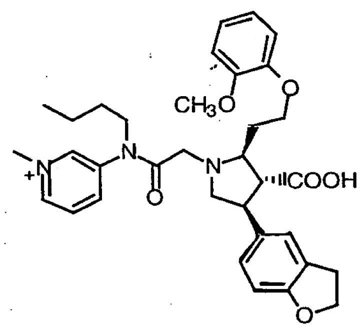

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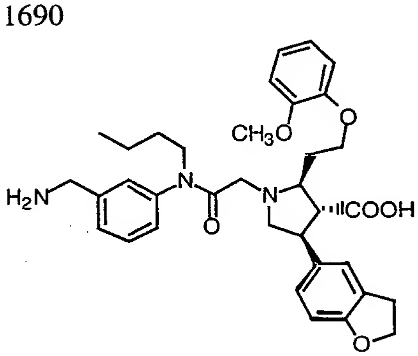

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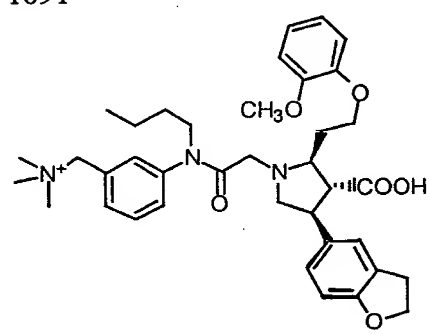

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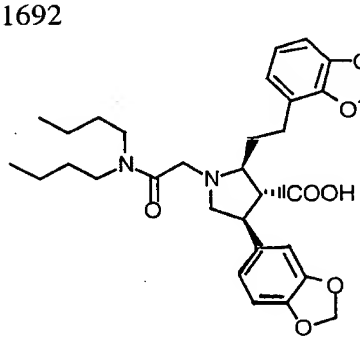

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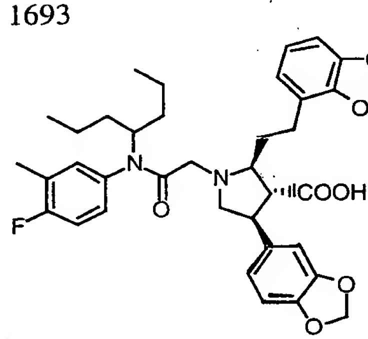

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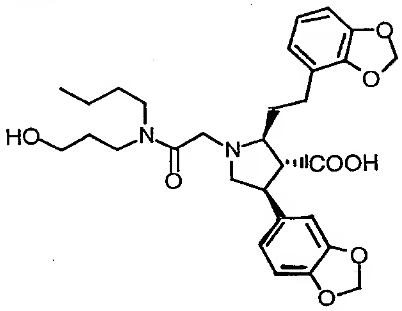

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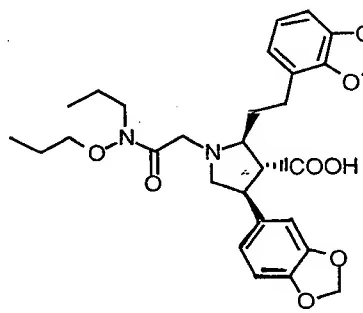

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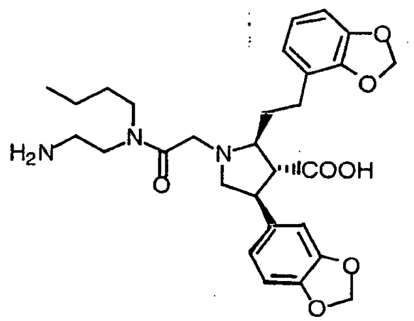

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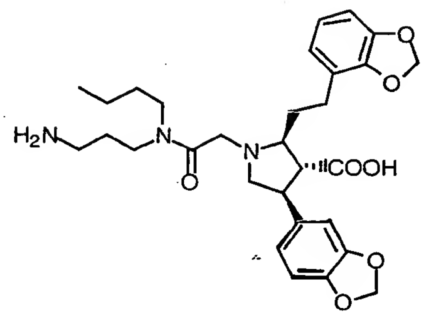

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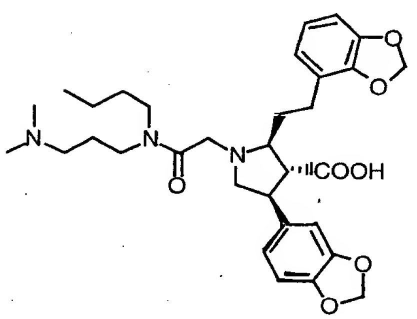

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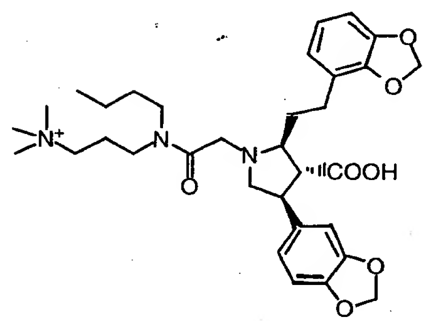

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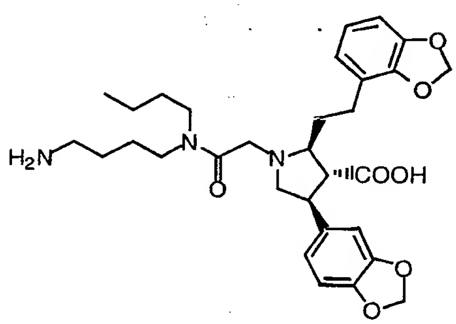

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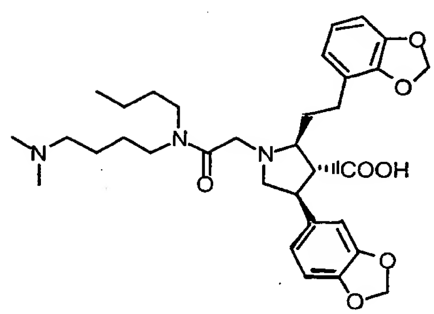

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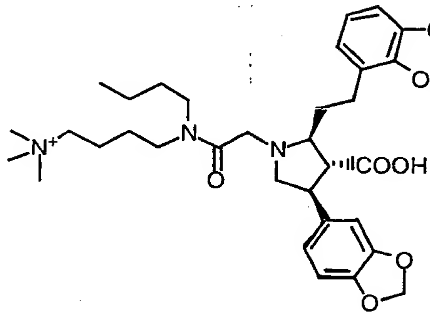

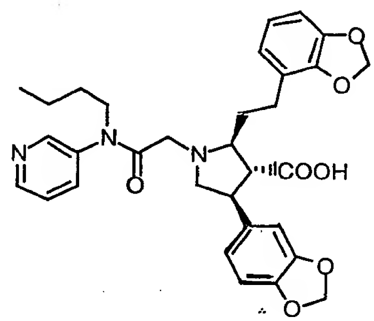

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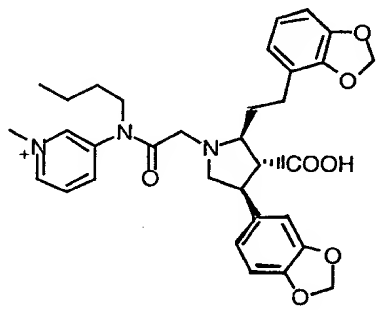

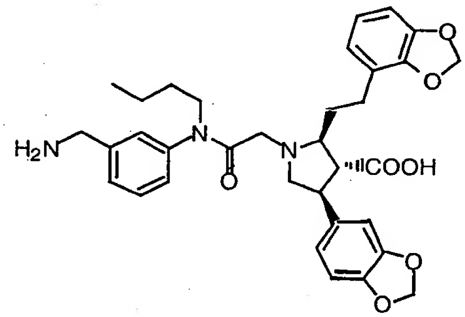

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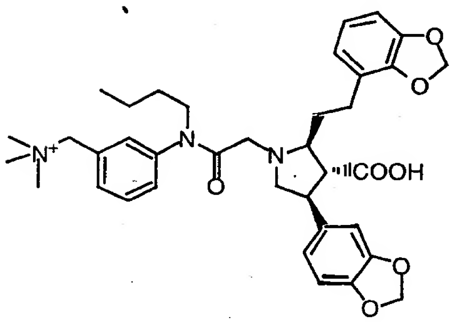

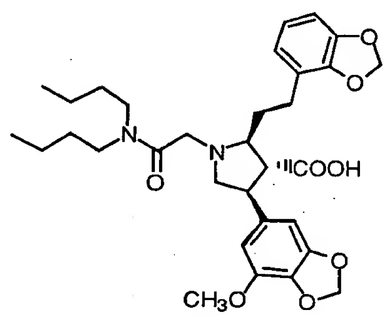

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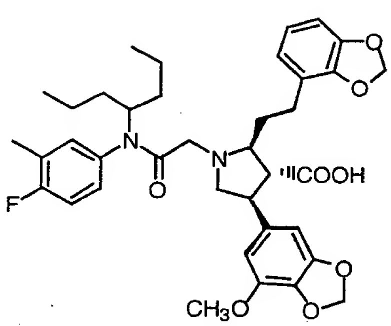

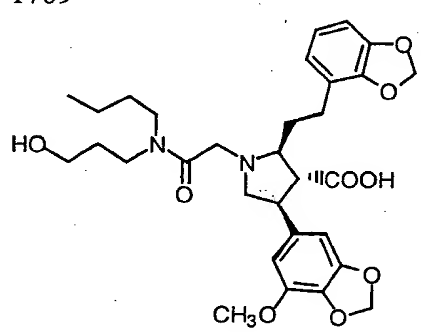

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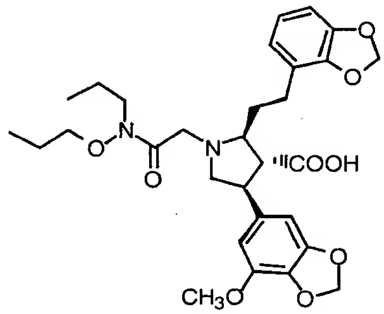

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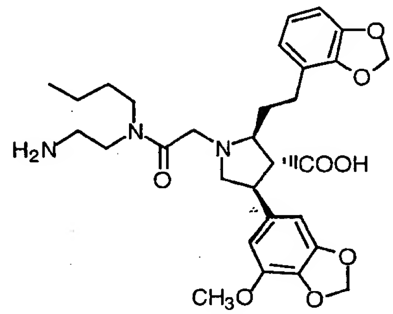

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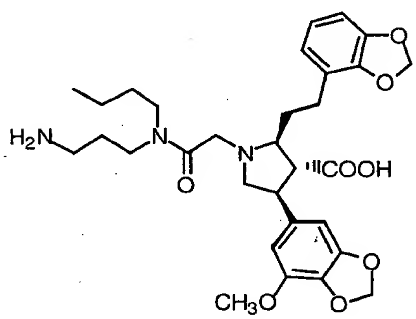

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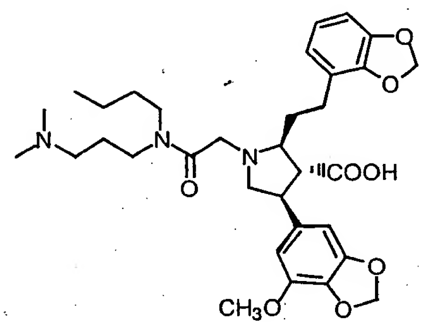

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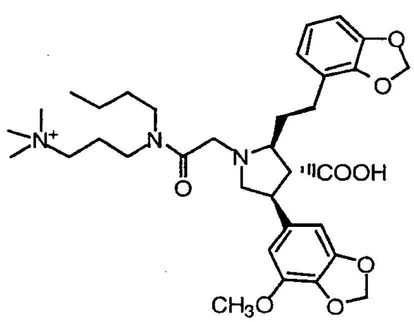

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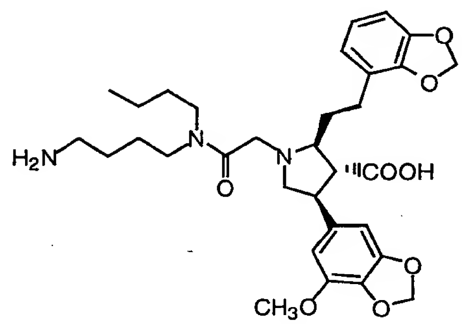

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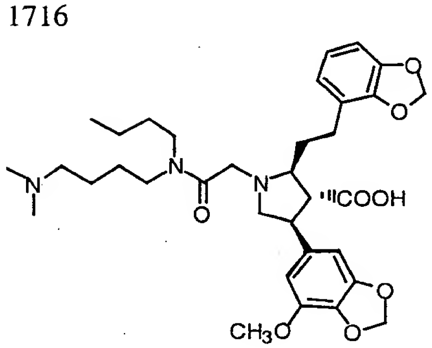

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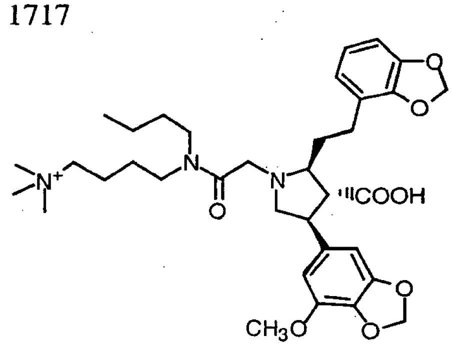

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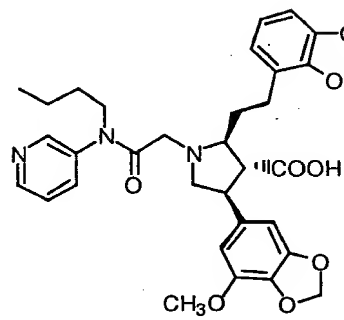

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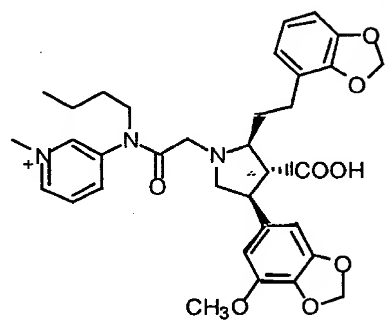

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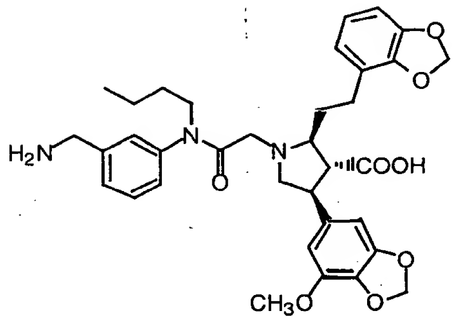

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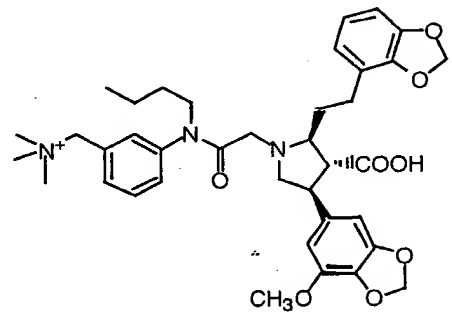

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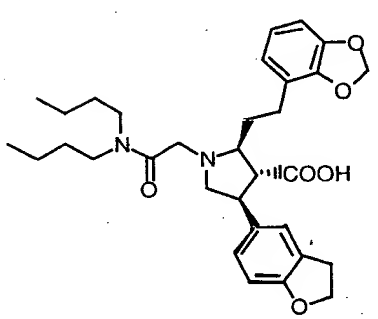

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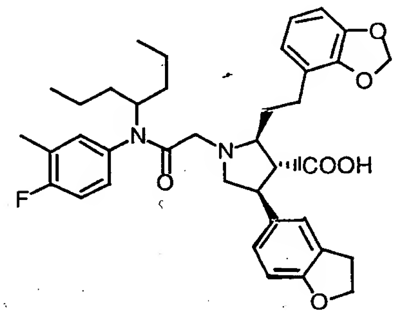

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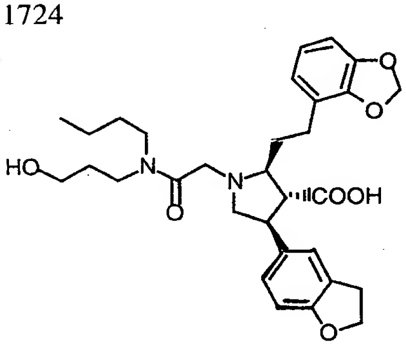

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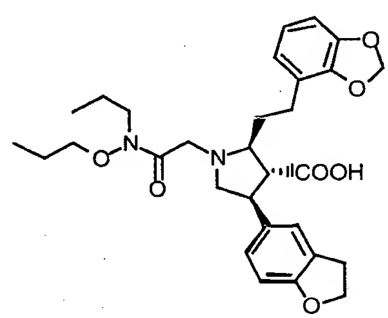

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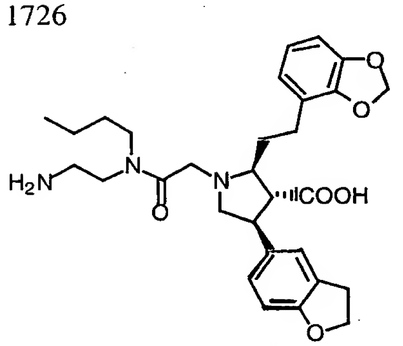

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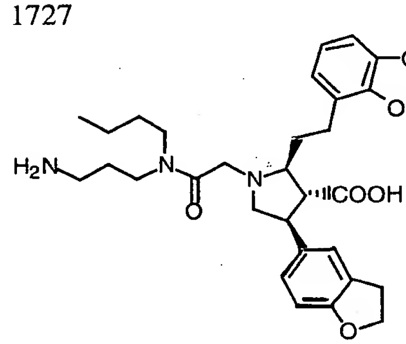

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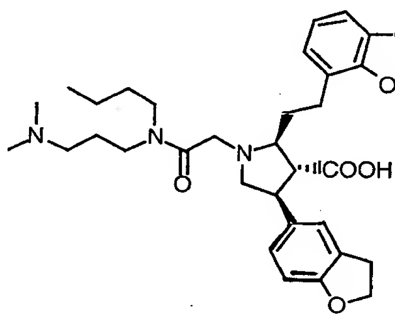

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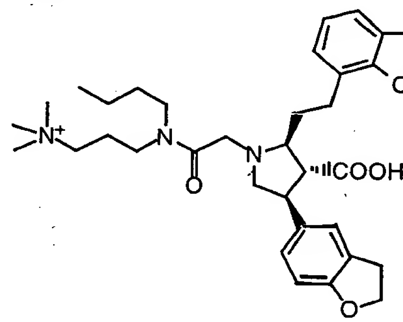

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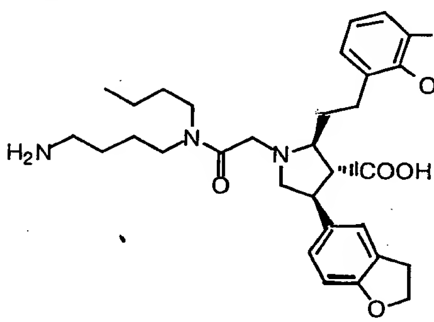

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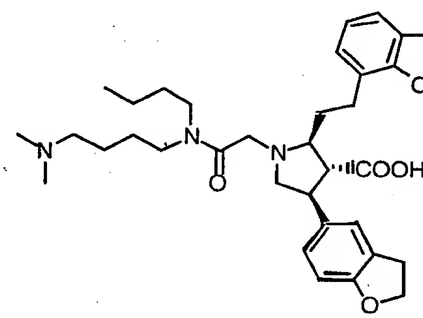

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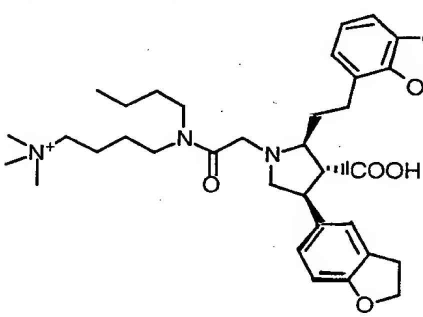

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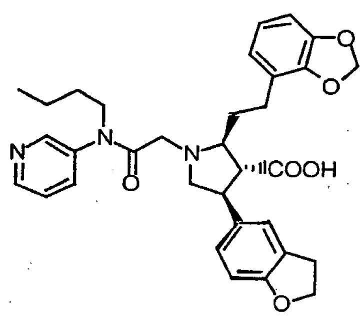

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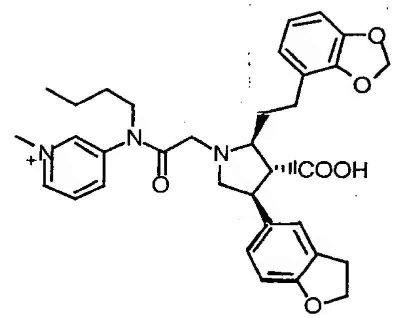

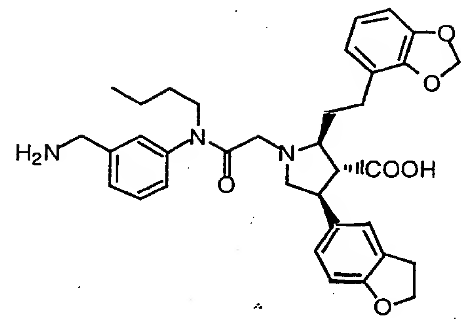

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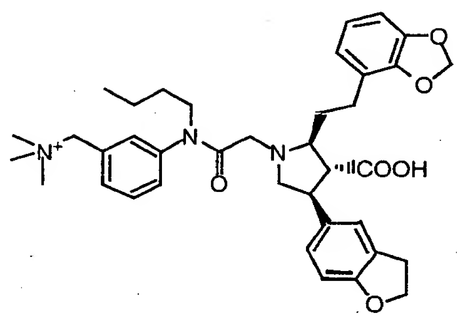

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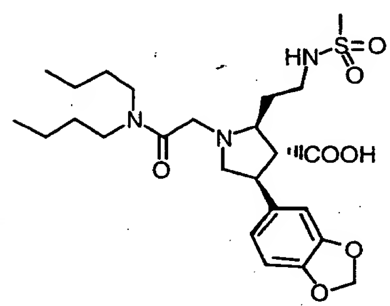

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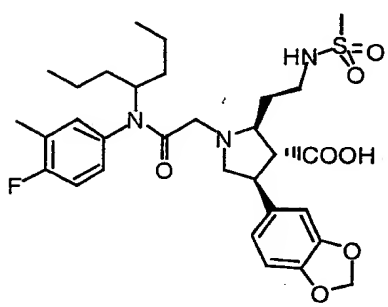

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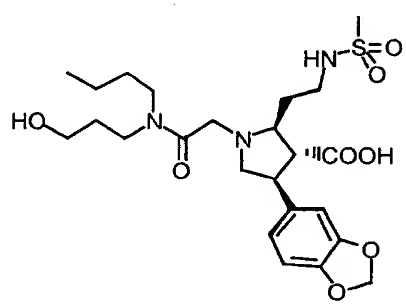

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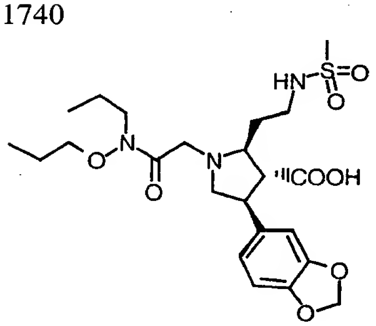

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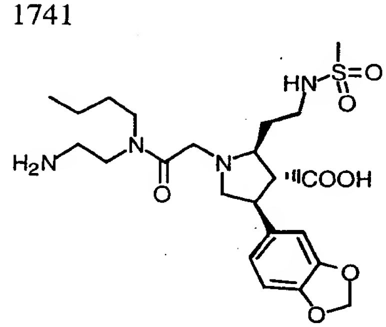

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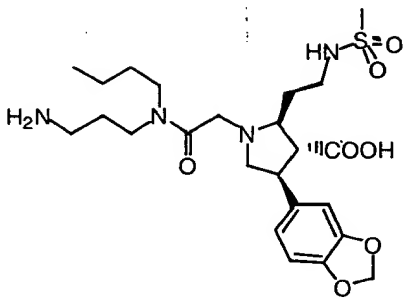

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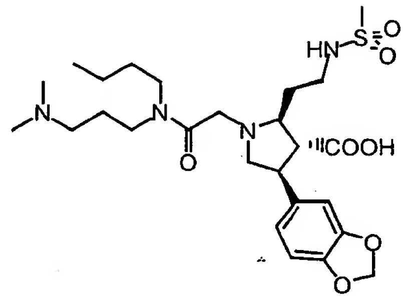

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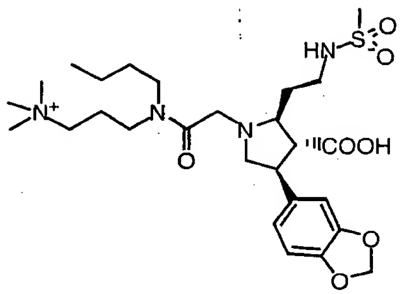

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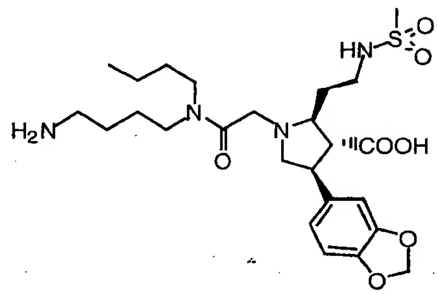

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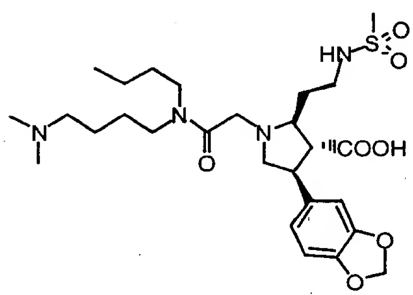

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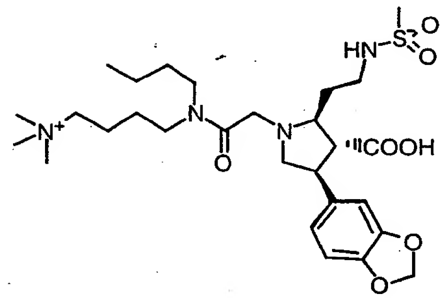

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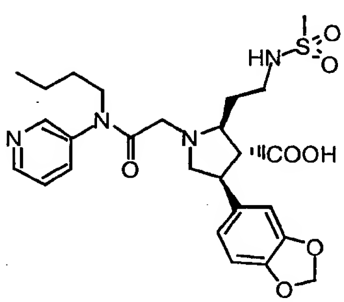

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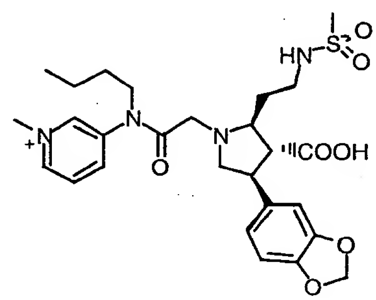

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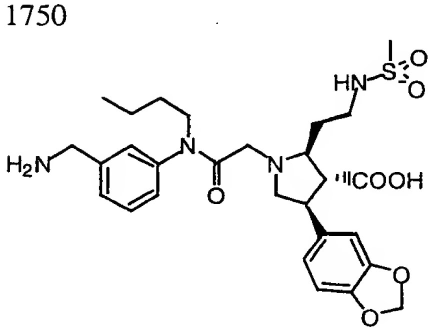

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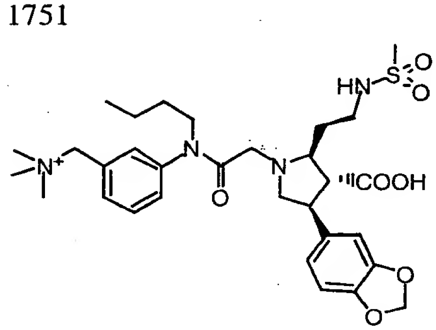

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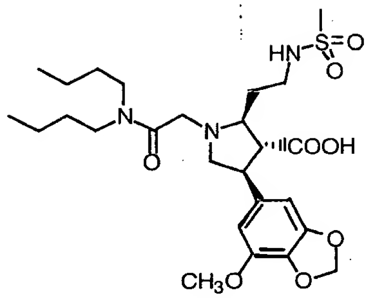

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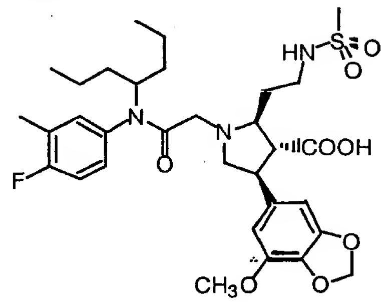

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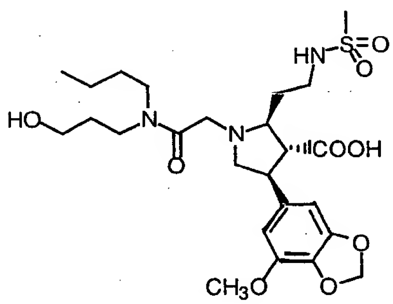

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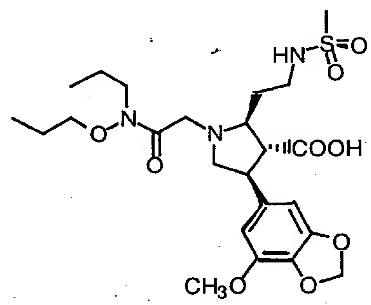

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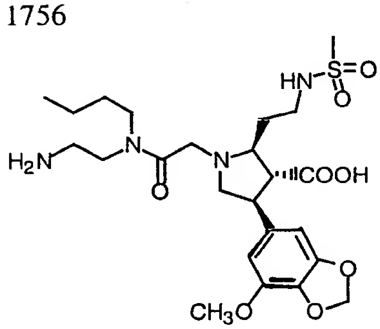

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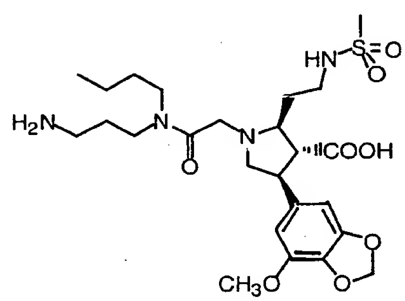

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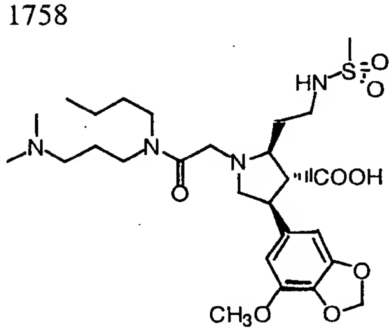

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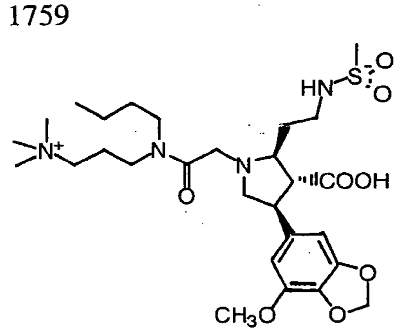

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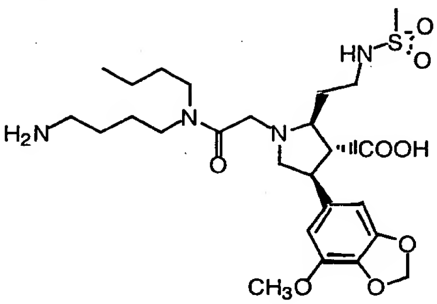

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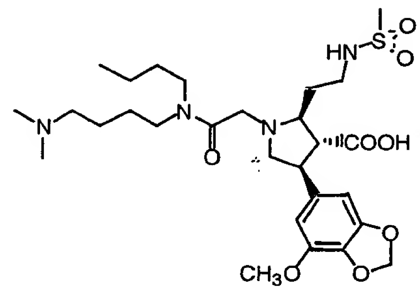

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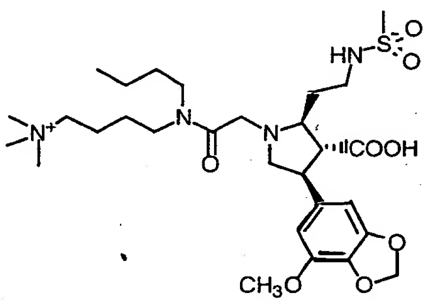

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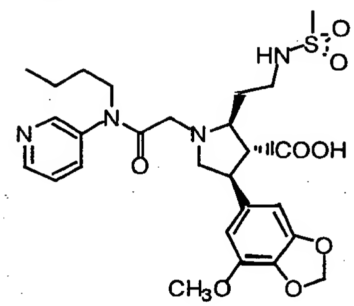

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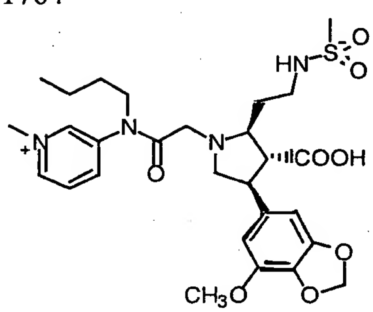

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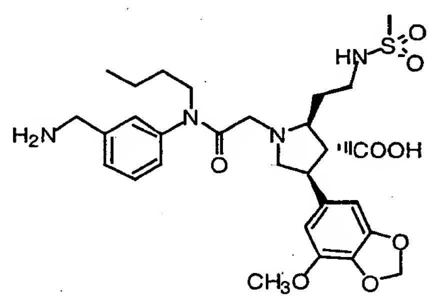

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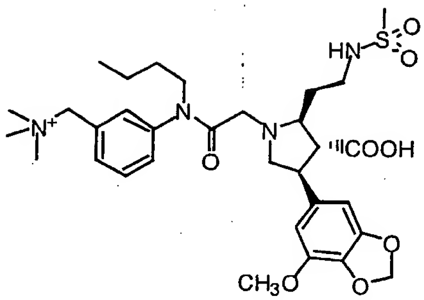

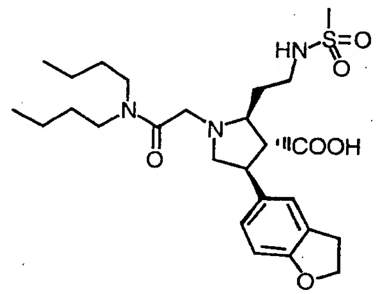

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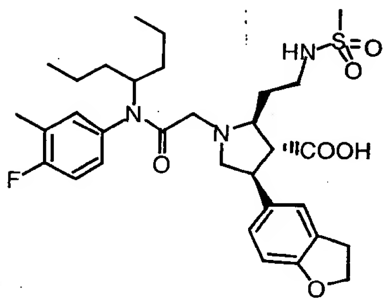

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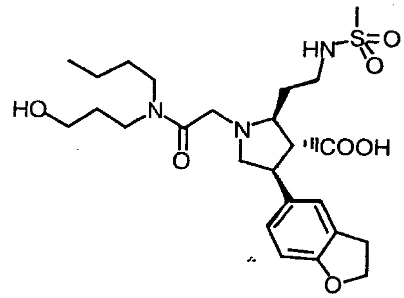

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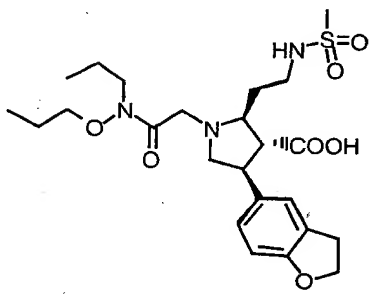

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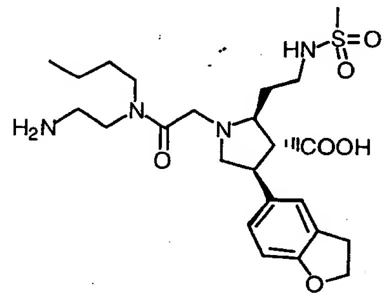

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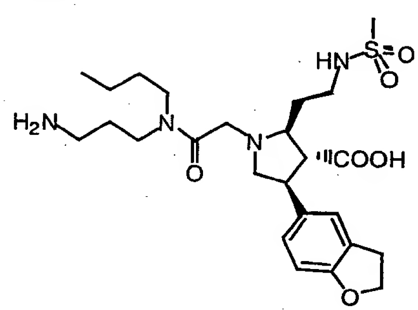

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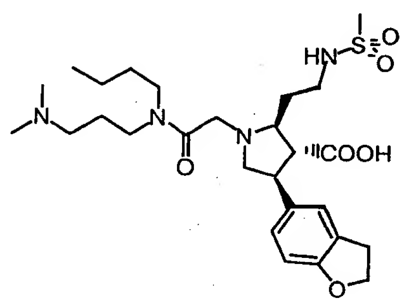

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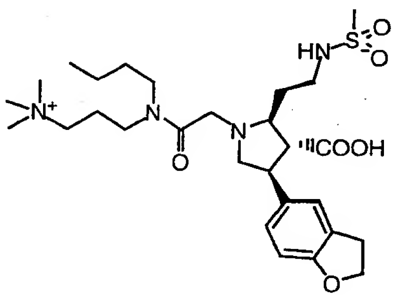

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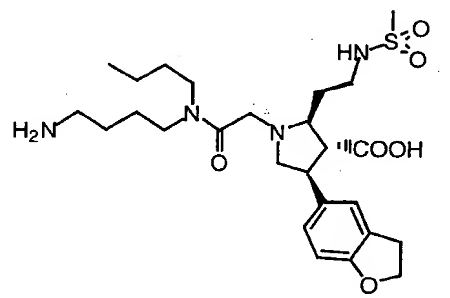

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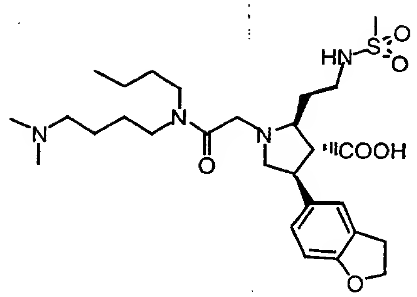

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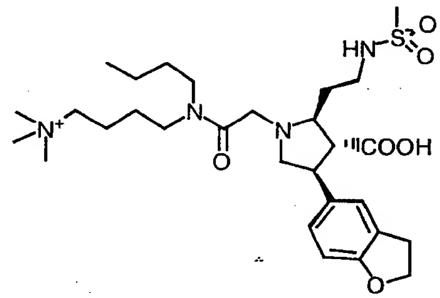

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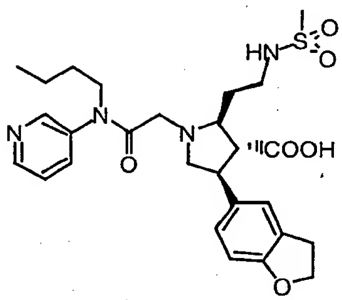

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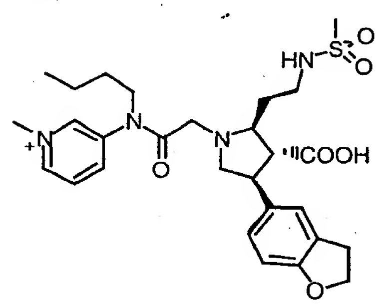

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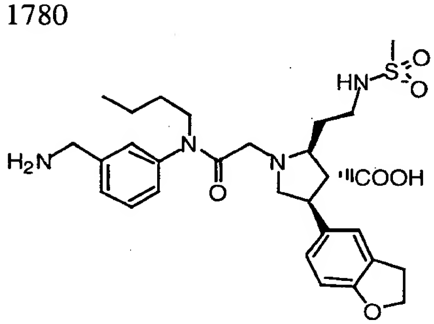

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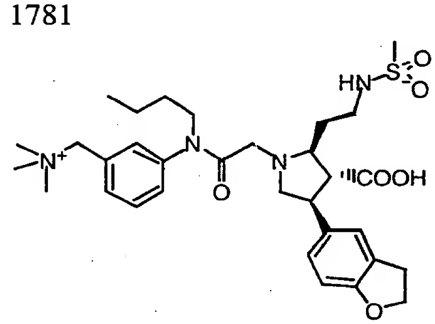


Example 536

(*2S,3R,4S*)-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 536A

Ethyl 5,5-dimethyl-3-oxooctanoate

Ethyl 3,3-dimethylhexanoate was prepared using the general procedure of Cahiez *et al.*, Tetrahedron Lett., 31, 7425 (1990). To a solution of

63.8 g (370 mmol) of this compound in 400 mL of ethanol, cooled to 0°C, was added a solution of 30 g of NaOH in 150 mL of water. The resultant solution was warmed to ambient temperature and stirred overnight. Solvents were removed in vacuo; the residue was taken up in 700 mL of water, and extracted twice with 1:1 ether/hexanes. The aqueous layer was acidified to pH3 with 1N HCl and extracted twice with hexanes. The combined hexane extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. A 20.2 g (150 mmol) sample of the crude product is dissolved in 150 mL of THF; 27.3 g of 1,1′-carbonyldiimidazole is added portionwise, to control gas evolution. In meantime, 33.4 g of potassium ethylmalonate and 13.4 g of magnesium chloride are combined in 350 mL of THF (overhead mechanical stirring) and warmed to 50°C for 3 hrs. This mixture is cooled to ambient temperature, and the above acid imidazolide solution is added. The resultant slurry is stirred overnight. Ether (600 mL), hexanes (600 mL) and aqueous 1N phosphoric acid (500 mL) are added, and the mixture is sitrred for 30 min. The aqueous layer is separated; the organics are washed sequentially with bicarb (2X), water and brine. The organics are dried over sodium sulfate, filtered and concentrated to give 30.2 g (95% yield) of a colorless liquid.

Example 536B

4-Methoxy-6-(2-nitrovinyl)-1,3-benzodioxole

3-Methoxypiperonal (50.0 g) is combined with 71.9 mL of nitromethane in 250 mL of acetic acid; 36 g of ammonium acetate is added, and the mixture is heated to 50°C for 4 hrs. Solvents are removed in vacuo; the residue is taken up in water and stirred for 20 min. The solution is filtered; the filtrate is washed with water, then ether, to give 51.8 g of a yellow solid.

Example 536C

Ethyl *trans, trans*-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate

The compound of Example 536A (6.42 g, 30 mmol) was combined with 5.79 g of the compound of Example 536B in 40 mL of THF. DBU (0.5 mL) was added, and the mixture was stirred at ambient temperature for 6 hrs, during which time it turns reddish brown, and homogeneous. The solvents were removed in vacuo; the residue was taken up in EtOAc and washed

sequentially with aqueous 1N phosphoric acid and brine. The organic phase was dried over sodium sulfate, filtered and concentrated. The residue was dissolved in 50 mL of THF; 12 g of Raney Nickel catalyst (washed sequentially with water and ethanol) was added, followed by 10 mL of acetic acid. The resultant mixture was hydrogenated under 4 atmospheres of hydrogen until hydrogen uptake ceased (~ 3 hrs). The catalyst was removed by filtration; solvents were removed in vacuo. The residue was dissolved in 90 mL of 2:1 ethanol/THF; 30 mg of bromcresol green indicator was added, followed by 30 mL of 1N sodium cyanoborohydride in THF. Concentrated HCl was added dropwise to maintain pH at the indicator point, over 1 hr. The resultant solution was stirred overnight at ambient temperature. Bicarb was added, and the solvents were removed in vacuo; the residue was partitioned between water and EtOAc. The organic material was washed with water (2X) and brine. The organic phase was dried over sodium sulfate, filtered and concentrated. The crude product was dissolved in 100 mL of acetonitrile; 10 mL of Hünig's base was added, and the solution was warmed to 40°C overnight. Removal of solvents in vacuo provided 5.0 g of a yellowish oil.

Example 536D

Ethyl (*2S,3R,4S*)-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate

The crude compound of Example 536C (2.0 g) was combined with 4 mL of triethylamine in 40 mL of THF; 2.0 g of di-*tert*-butyldicarbonate was added, and the mixture was stirred at ambient temperature for 5 hrs. Solvents were removed in vacuo, and the residue was taken up in 60 mL of ethanol. Aqueous sodium hydroxide (10 mL of 2.5 N solution) was added, and the resultant solution was stirred overnight. Solvents were removed in vacuo; the residue was taken up in water and extracted with ether. The aqueous phase was acidified with aqueous 1N phosphoric acid and extracted with EtOAc. The organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated to give 1.0 g of a colorless oil. A sample of this material (0.734 g, 1.58 mmol) was combined with 0.35 g of pentafluorophenol and 0.364 g of EDAC in 5 mL of DMF. The resultant solution was stirred at ambient temperature for 1 hr, then was poured onto 50 mL of 0.6M sodium bicarbonate solution and extracted (3 X 15 mL) with ether. The combined ether extracts were washed with brine, dried over magnesium sulfate, filtered,

and concentrated in vacuo to give a foam, which was dissolved in 5 mL of THF and cooled to 0°C. Simultaneously, 0.418 g (2.37 mmol) of R-4-benzyl-2-oxazolidinone was combined with ~0.1 mg of pyreneacetic acid in 5 mL of THF and cooled to 0°C. N-butyllithium (1.6M in hexanes) was added to a red endpoint (persists ~10 sec), and the solution was stirred for 10 min. The solution was transferred into the solution of the pentafluorophenyl ester, and the resultant solution was stirred at 0°C for 40 min. Solvents were removed in vacuo; the residue was taken up in bicarb and extracted with ether (3 X 10 mL). The combined ether extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude mixture of diasteromeric products was separated by flash chromatography on silica gel, eluting with a gradient from 4:1->3:1->2:1 hexanes/EtOAc, giving 423 mg of the faster-moving and 389 mg of the slower-moving diastereomer, respectively. The faster-moving diastereomer was dissolved in 2 mL of a 2.0M solution of sodium methoxide in methanol (freshly prepared, containing 5% methyl formate by volume) and stirred at ambient temperature for 16 hrs. Solvents were removed in vacuo, and the residue was partitioned between ether and aqueous 1N sodium hydroxide. The ether layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel, eluting with 4:1 hexanes/EtOAc. The resultant material was dissolved in 5 mL of TFA and stirred at ambient temperature for 1 hr. Solvents were removed in vacuo; the residue was suspended in bicarb and extracted with EtOAc. The organic phase was washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to give 98 mg of product.

Example 536E

(2S,3R,4S)-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The compound of Example 536D (48 mg) was combined with 35 mg of the compound of Example 501A in 3 mL of acetonitrile; 0.5 mL of Hünig's base was added, and the solution was allowed to stir overnight at ambient temperature. Solvents were removed in vacuo; the residue was partitioned between EtOAc and aqueous 1N phosphoric acid. The organic layer was washed with bicarb and brine, then dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica

gel, eluting with 2:1 hexanes/EtOAc. The product was dissolved in 4 mL of ethanol; 1 mL of 2.5N aqueous sodium hydroxide was added, and the resultant solution was stirred overnight at ambient temperature. Solvents were removed in vacuo; the residue was taken up in water and extracted with ether. The aqueous phase was acidified to pH 3 with aqueous 1N phosphoric acid and extracted with EtOAc. The organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated to give a colorless oil. Lyophilization from acetonitrile/0.1% aqueous TFA gave 56 mg of a white solid.

^1H NMR ($CDCl_3$, 300 MHz) d 0.81 (s, 3H), 0.84 (s, 3H), 0.86 (t, J = 6.9 Hz, 3H), 0.93 (t, J = 6.9 Hz, 3H), 0.96 (t, J = 6.9 Hz, 3H), 1.09-1.38 (m, 8H), 1.45-1.59 (m, 4H), 1.84-2.00 (m, 2H), 3.15 (dd, J = 6.9 Hz, 10.0 Hz, 2H), 3.30-3.42 (m, 3H), 3.72 (t, J = 10.5 Hz, 1H), 3.86 (t, J = 10.5 Hz, 1H), 3.88 (s, 3H), 4.02 (q, J = 10.0 Hz, 1H), 4.12 (d, J = 16.8 Hz, 1H), 4.29 (d, J = 16.8 Hz, 1H), 4.41 (brm, 1H), 5.94 (s, 1H), 6.52 (d, J = 1.8 Hz, 1H), 6.67 (d, J = 1.8 Hz, 1H). MS (ESI) $(M+H)^+$ at m/e 533. Anal calcd for $C_{30}H_{48}N_2O_6 \cdot 0.7$ TFA: C, 61.57; H, 8.01; N, 4.57. Found: C, 61.59; H, 8.20; N, 4.63.

Example 537

(2S,3R,4S)-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 537A

Ethyl *trans, trans*-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate

Prepared according to the procedures of Example 536C above, substituting the compound of Example 501B (5-(2-nitrovinyl)-1,3-benxodioxole) for 4-methoxy-6-(2-nitrovinyl)-1,3-benzodioxole.

Example 537B

Ethyl (2S,3R,4S)-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate

The compound of Example 537A (6.8 g) was dissolved in 100 mL of ether; a solution of 1.6 g of (S)-(+)-mandelic acid in 60 mL of ether was added, the total volume was made up to ~200 mL, and the solution was seeded. The mixture was stirred slowly overnight. The resultant crystals were collected by

filtration and recrystallized from ether/EtOAc to give 1.8 g of a white solid. Thsi material was partitioned between bicarb and ether; the ether layer was washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo to give the enantiomerically pure product (>98% e.e.).

Example 537C

(2S,3R,4S)-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Prepared from the compound of Example 537B according to the procedures of Example 536E. ^{1}H NMR ($CDCl_3$, 300 MHz) d 0.80-0.99 (m, 15H), 1.10-1.37 (m, 8H), 1.43-1.58 (m, 4H), 1.77-1.97 (m, 2H); 3.48-3.12 (m, 5H), 3.60-3.69 (m, 1H), 3.75-3.86 (m, 1H), 3.95-4.16 (m, 2H), 4.28-4.4 (m, 2H), 5.94 (s, 2H), 6.74 (d, J=7.8 Hz, 1H), 6.8 (dd, J=8.1, 1.5 Hz, 1H), 6.87 (d, J=1.8 Hz, 1H). MS (APCI+) m/e 503 $(M+H)^+$.

Example 538

(2S,3R,4S)-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-1-((N-propoxy, N-(n-butyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 538A

N-Boc-N-butyl-O-allylhydroxylamine

O-Allylhydroxylamine hydrochloride hydrate (5.0g) was dissolved in THF (15 mL). The solution was cooled to 0°C in an ice bath. Diisopropylethylamine (8mL) and di-t-butyldicarbonate (10.0g) were added. The mixture was stirred at 0°C for one hour at which point the bath was removed and the reaction allowed to warm to room temperature and stirred overnight. The THF was removed *in vacuo* and the residue taken up in EtOAc (25 mL), and washed with water (1 x 50 mL), saturated sodium bicarbonate solution (3 x 50 mL), 1N phosphoric acid (3 x 50 mL), and brine (1 x 50 mL). The organic layer was dried with sodium sulfate and evaporated to give a light yellow oil (6.5g). This crude product was dissolved in dry THF (25 mL) and the solution cooled to 0°C in an ice bath. Sodium hydride (1.5g, 60% dispersion in oil) was added portionwise over five minutes. The resulting mixture was stirred for 30 minutes at 0°C. 1-Iodobutane (4.1 mL) was added dropwise to the mixture. The reaction was stirred at 0°C for one hour, then stirred overnight at room temperature. The THF was removed *in vacuo* and the residue taken up in EtOAc (50 mL) and washed with water (1 x 50 mL), saturated sodium bicarbonate solution (3 x 50 mL), 1N phosphoric acid (3 x 50 mL), and brine (1 x 50 mL). The organic layer was dried with sodium sulfate and evaporated to give a light yellow oil, which

was purified by flash chromatography on silica gel eluting with 5% EtOAc/hexanes to give the title compound as a colorless oil (6.0 g).

Example 538B

N-butyl-N-propoxyamine trifluoroacetate

The compound of Example 538A (6.0 g) was dissolved in EtOAc (100 mL). 10% Palladium-on-carbon (0.5 g) was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at room temperature for 6 hours. The catalyst was removed by filtration through a pad of Celite and the solvents were removed *in vacuo* to give a yellow oil which was purified by flash chromatography on silica gel eluting with 5% EtOAc/hexanes to give a colorless oil (5.8 g). A sample of the resultant material (1.15 g) was dissolved in CH_2Cl_2 (5 mL) and cooled in an ice bath. Trifluoroacetic acid (3mL) was added and the solution stirred cold for two hours. The solvent was removed *in vacuo* , care being taken not to allow the solution to warm above room temperature. The residue contained considerable TFA and was used without further purification.

Example 538C

N-butyl-N-propoxy-bromoacetamide

The salt of Example 538B (0.60 g) was dissolved in acetonitrile (5 mL) and cooled to -20°C. Hünig's base (5.5 mL) was added slowly. Bromoacetyl bromide (0.5 mL) was added dropwise over five minutes. The solution was stirred at -20°C for 30 minutes. The bath was removed and the solution was stirred for six hours at room temperature. The solvent was removed *in vacuo* and the residue taken up in EtOAc (50 mL) and washed with water (1 x 25 mL), 1N phosphoric acid (3 x 25 mL), and brine (1 x 25 mL). The organic layer was dried with sodium sulfate and evaporated to give a dark orange oil (0.65 g) which was used without further purification.

Example 538D

(*2S,3R,4S*)-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-1-((N-propoxy, N-(n-butyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The compound of Example 537B was reacted with the compound of Example 538C according to the procedures of Example 536E.

Example 539

(2S,3R,4S)-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-1-((N-propoxy, N-(n-propyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 539A

N-propyl-N-propoxy bromoacetamide

Prepared according to the procedures of Example 538A-C, substituting iodopropane for iodobutane in Example 538A.

Example 539B

(2S,3R,4S)-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-1-((N-propoxy, N-(n-propyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The compound of Example 537B was reacted with the compound of Example 539A according to the procedures of Example 536E.

Example 540

(2S,3R,4S)-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((N-propoxy, N-(n-butyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The compound of Example 536D was reacted with the compound of Example 538C according to the procedures of Example 536E.

Example 541

(2S,3R,4S)-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((N-propoxy, N-(n-propyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The compound of Example 536D was reacted with the compound of Example 539A according to the procedures of Example 536E.

Example 542

(2S,3R,4S)-2-(2,2-Dimethylpent-3-enyl)-4-(1,3-benzodioxol-5-yl)-1-((N-propoxy, N-(n-butyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 542A

trans-Ethyl 3,3-dimethyl-4-hexenoate

A mixture of 4-methyl-3-penten-2-ol (7.4 g, 74 mmol), triethyl orthoacetate (13.6 mL, 74mmol) and propionic acid (0.28 mL, 3.7 mmol) was heated at 150°C for 7 hr. The product was then distilled under normal pressure (200-220 °C) to give 5.0 g of crude ester as a colorless oil.

Example 542B

Ethyl *trans,trans*-2-(2,2-Dimethylpent-3-enyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate

The title compound is prepared according to the procedures of Examples 536A and 536C, substituting the compound of Example 542A for ethyl 3,3-dimethylhexanoate in Example 536A and the compound of Example 501B (5-(2-nitrovinyl)-1,3-benxodioxole) for 4-methoxy-6-(2-nitrovinyl)-1,3-benzodioxole in Example 536C.

Example 542C

Ethyl (2S,3R,4S)-2-(2,2-Dimethylpent-3-enyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate

The compound of Example 542B was resolved according to the procedure described in Example 537B.

Example 542D

(2S,3R,4S)-2-(2,2-Dimethylpent-3-enyl)-4-(1,3-benzodioxol-5-yl)-1-((N-propoxy, N-(n-butyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The compound of Example 542C was reacted with the compound of Example 538C according to the procedures of Example 536E.

Example 543

(*2S,3R,4S*)-2-(2,2-Dimethylpent-3-enyl)-4-(1,3-benzodioxol-5-yl)-1-((N-propoxy, N-(n-propyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The compound of Example 542C was reacted with the compound of Example 539A according to the procedures of Example 536E.

Example 544

(*2S,3R,4S*)-2-(2,2-Dimethylpent-3-enyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((N-propoxy, N-(n-butyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 544A

Ethyl *trans,trans*-2-(2,2-Dimethylpent-3-enyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate

The title compound is prepared according to the procedures of Examples 536A and 536C, substituting the compound of Example 542A for ethyl 3,3-dimethylhexanoate in Example 536A.

Example 544B

Ethyl (*2S,3R,4S*)-2-(2,2-Dimethylpent-3-enyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate

The compound of Example 544A was resolved according to the procedure described in Example 536D.

Example 544C

(*2S,3R,4S*)-2-(2,2-Dimethylpent-3-enyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((N-propoxy, N-(n-butyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The compound of Example 544B was reacted with the compound of Example 538C according to the procedures of Example 536E.

Example 545

(*2S,3R,4S*)-2-(2,2-Dimethylpent-3-enyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((N-propoxy, N-(n-propyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The compound of Example 544B was reacted with the compound of Example 539A according to the procedures of Example 536E.

Example 546

(*2S,3R,4S*)-2-(2-(2-pyridyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-((*N*-4-heptyl-*N*-(2-methyl-3-fluorophenyl)) amino carbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 546A

Ethyl *trans,trans*-2-(2-(2-pyridyl)ethyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate

The title compound is prepared according to the procedures of Examples 536A and 536C, substituting the compound of Example 519A for 3,3-dimethylhexanoic acid in Example 536A.

Example 546B

Ethyl (*2S,3R,4S*)-2-(2-(2-pyridyl)ethyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate

The compound of Example 546A (1.5 g) was dissolved in CH_2Cl_2 (25 mL). Di-t-butyldicarbonate (0.9 g) was added and the solution stirred overnight at room temperature. The solvent was evaporated *in vacuo* and the residue taken up in EtOAc (50 mL), washed with water (1x50 mL), saturated sodium bicarbonate solution (3x50 mL), and brine (1x50 mL). The organic layer was dried with sodium sulfate and evaporated *in vacuo* to give an oil with was purified by flash chromatography on silica gel eluting with 1/10/10 EtOH/EtOAc/hexanes to give a colorless oil (1.5 g). The oil was dissolved in EtOH (10 mL) and 50% NaOH solution (0.5 mL) and water (5 mL)

were added. The mixture was stirred overnight at room temperature. The solvents were evaporated *in vacuo* and the residue taken up in EtOAc (25 mL) and acidified with 1 N H_3PO_4 (10 mL). The layers were separated and the organic layer dried with sodium sulfate and evaporated to give a white semi-solid (1.3 g). A sample of the resultant Boc-protected amino acid (0.9 g) was dissolved in DMF (5 mL). (S)-Phenylalaninol (0.32 g), HOOBt (0.33 g), and EDCI (0.40 g) were added and the solution sitrred overnight at room temperature. Water (50 mL) was added and the mixture extracted with EtOAc (3x25 mL). The organic layers were combined, washed with water (2x50 mL), saturated sodium bicarbonate solution (3x50 mL), and brine (1x50 mL), and evaporated to give a yellow oil; tlc indicated the presence of two diastereomeric products. The diastereomeric amides were separated by flash chromatography on silica gel eluting with 1/12/12 EtOH/EtOAc/hexanes to give faster- (450 mg) and slower-moving isomers (400 mg). The faster-moving diastereomer (400 mg) was taken up in 6N HCl and heated at reflux overnight. The solvent was evaporated and the residue was taken up in toluene (75 mL) and evaporated. This was repeated two additional times to give a brown solid, which was dissolved in EtOH (50mL). 4N HCl/dioxane (10 mL) was added and the solution heated at reflux overnight. The EtOH was evaporated and the residue taken up in EtOAc which was treated with saturated sodium bicarbonate solution (3x50 mL), and brine (1x50 mL), and evaporated to give a brown solid. Flash chromatography on silica gel eluting with 30% EtOH/EtOAc gave a mixture of products (130mg) which was approximately 70% desired material. This product was carried forward without additional purification.

<u>Example 546C</u>

<u>*(2S,3R,4S)*-2-(2-(2-pyridyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-((*N*-4-heptyl-*N*-(2-methyl-3-fluorophenyl)) amino carbonylmethyl)-pyrrolidine-3-carboxylic acid</u>

The compound of Example 546B was reacted with the compound of Example 508E according to the procedures of Example 536E.

<u>Example 547</u>

<u>*(2S,3R,4S)*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl)-pyrrolidine-3-</u>

carboxylic acid

Example 547A
N-butyl-4-hydroxybutyramide

To 30 mL (390 mmol) of g-butyrolactone was added 45 ml (455 mmol) of *n*-butylamine. The solution was heated at 85°C for 1.5 hr, then the excess n-butylamine was removed *in vacuo*. The product crystallized on standing to give about 62 g of a colorless, low melting solid.

Example 547B
N-butyl-4-hydroxybutyl chloroacetamide

To an ice cooled solution of 3.40 g (91.9 mmol) of $LiAlH_4$ in 90 mL of THF was added 2.4 mL of 98% H_2SO_4, dropwise, with stirring. After bubbling had ceased, a solution of 4.7 g of the compound of Example 547A in 10mL of THF was added. The mixture was stirred at reflux for 24 hr, then cooled with an ice bath and quenched by sequential dropwise addition of 1.7 mL H_2O, and 17 mL of 25% *w/v* aqueous NaOH. The white precipitate was filtered, and washed with about 50 mL of THF. The combined filtrate and washings were concentrated to 3.85 g of an oil. To an ice cooled solution of this material in 35 mL of ethyl acetate was added a solution of 5.0 g (29.2 mmol) of chloroacetic anhydride in 10 mL of ethyl acetate. The solution was stirred at 0°C for 30 min, then extracted with saturated aqueous $NaHCO_3$ solution (1 x 25 mL), 2M NaOH (1 x 25 mL), 5% NH_4OH (1 x 25 mL), 1M HCl (1 x 25 mL), and brine (1 x 25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to an oil. The product was purified *via* silica gel chromatography, eluting with 98:2 diethyl ether: methanol, to give 1.52 g (31%) of a colorless oil.

Example 547C
Ethyl (*2S,3R,4S*)-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((N-butyl-N-(4-hydroxybutyl)amino)carbonylmethyl)-pyrrolidine-3-carboxylate

To 1.52 g (6.85 mmol) of the compound of Example 547B was added 2.75 g (7.44 mmol) of the ethyl (*2S,3R,4S*)-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate (prepared by neutralization of the

compound of Example 501G), 10 mL of DMSO, and 2 mL of N,N-diisopropylethylamine. The solution was stirred at ambient temperature for 22 h, then poured into 100 mL of water and extracted with diethyl ether (3 x 25 mL). The combined ether layers were washed with water (1 x 25 mL), 4% (*v/v*) H_3PO_4 (1 x 25 mL), saturated aqueous $NaHCO_3$ solution (1 x 25 mL), and brine (1 x 25 mL), dried over $MgSO_4$, filtered, and concentrated to an oil. This was purified *via* silica gel chromatography, eluting with 98:2 diethyl ether: methanol to give 3.0g (79%) of a colorless oil.

Example 547D

Ethyl (*2S,3R,4S*)-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((N-butyl-N-(4-bromobutyl)amino)carbonylmethyl)-pyrrolidine-3-carboxylate

To an ice cooled solution of 2.80 g (5.05 mmol) of the compound of Example 547C in 27 mL of diethyl ether was added 1.4 mL (10 mmol) of triethylamine, then 0.58 mL of methanesulfonyl chloride. A white precipitate formed, and the suspension was stirred at 0 °C for 20 min. The reaction was diluted with 75 mL of diethyl ether, then extracted with saturated aqueous $NaHCO_3$ solution (2 x 25 mL), 5% NH_4OH (2 x 25 mL), and brine (1 x 25 mL), dried over $MgSO_4$, filtered, and concentrated to 3.0 g of a colorless oil. To this material in 45 mL of DMF was added 6.0 g (69 mmol) of LiBr. The reaction warmed to about 50 °C, then gradually cooled. The solution was stirred at ambient temperature for 4h, then poured into 450 mL of water, and extracted with diethyl ether (3 x 100 mL). The combined ether layers were back extracted with water (1 x 100 mL), and brine (1 x 100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to an oil. The product was purified via silica gel chromatography, eluting with 3:1 diethyl ether: petroleum ether, to give 2.65 g (90%) of a colorless oil.

Example 547E

(*2S,3R,4S*)-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid

To a solution of the compound of Example 547D (0.825 g, 1.34 mmol) in 3 mL of ethanol was added 5 mL of 4.07M dimethylamine in ethanol; the

resultant solution was heated at reflux for 75 min. Solvents were removed in vacuo. The residue was purified by flash chromatography on silica gel, eluting with 9:1 dichloromethane/methanol. The resultant material was taken up in 5 mL of 1.4N NaOH in 5:1 ethanol/water and stirred at ambient temperature for 14 hrs. Solvents were removed in vacuo; the residue was taken up in water, then adjusted to pH 6-7 with 1M HCl (~7 mL required). The mixture was extracted with EtOAc (3X); the aqueous layer was concentrated in vacuo. The residue was washed 3X with acetonitrile; the combined washes were filtered through Celite and concentrated to give 596 mg of a white foam.

Example 548

(*2S,3R,4S*)-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-1-((N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid

Prepared according to the procedures of Example 547, substituting the compound of Example 537B (ethyl (*2S,3R,4S*)-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate) in Example 547C.

Example 549

(*2S,3R,4S*)-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid

Prepared according to the procedures of Example 547, substituting the compound of Example 536D (ethyl (*2S,3R,4S*)-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate) in Example 547C.

Example 550

(*2S,3R,4S*)-2-(2,2-Dimethylpent-3-enyl)-4-(1,3-benzodioxol-5-yl)-1-((N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid

Prepared according to the procedures of Example 547, substituting the compound of Example 542C (ethyl (*2S,3R,4S*)-2-(2,2-Dimethylpent-3-enyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate) in Example 547C.

Example 551

(*2S,3R,4S*)-2-(2,2-Dimethylpent-3-enyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid

Prepared according to the procedures of Example 547, substituting the compound of Example 544A (ethyl (*2S,3R,4S*)-2-(2,2-Dimethylpent-3-enyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate) in Example 547C.

Example 552

(*2S,3R,4S*)-2-(2,2-Dimethylpent-3-enyl)-4-(1,3-benzodioxol-5-yl)-1-((N,N-di(nbutyl)amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid

Prepared according to the procedures of Example 1, substituting the compound of Example 541C (ethyl(*2S,3R,4S*)-2-(2,2-Dimethylpent-3-enyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate).

Example 553

(*2S,3R,4S*)-2-(2,2-Dimethylpent-3-enyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((N,N-di(n-butyl)amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid

Prepared according to the procesures of Example 1, substituting the compound of Example 544B (ethyl (*2S,3R,4S*)-2-(2,2-Dimethylpent-3-enyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate).

Example 554

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-((bis-(o-tolyl)methyl)amino)carbonylmethyl)-(pyrrolidine-3-carboxylic acid

Examples 554A through 554E

These compounds were prepared in Examples 501 B-F.

Example 554F

Bis-(o-tolyl)methylamine

In a 50 mL round-bottom flask were placed 2,2'-dimethylbenzophenone (prepared from commercially available methyl-2-methylbenzoate according to the procedure in *J. Chem. Soc.*, 1929, 1631) (2.50 g, 10 mmol), hydroxylamine hydrochloride (0.76 g, 11 mmol), pyridine (5mL) and ethanol (5 mL). The mixture was stirred under reflux for 8 h, cooled to r.t., diluted with EtOAc (25 mL) and transferred into a separatory funnel. The aqueous layer was removed, and organic layer was washed in turns with $CuSO_4$ (25 mL), water (25 mL) and brine (25 mL). After concentration of the organic phase, the residual oil obtained was purified by column chromatography (elution with 10 % EtOAc in Hexanes) to give 1.31 g (73%) of oxime as a white crystalline solid.

To 55 mL of ammonia cooled in a dry ice-acetone bath was added 130 mg (6 mmol) of sodium metal. To the resulting blue solution at -78 °C was added slowly 650 mg (3 mmol) of the above oxime in 25 mL of anhydrous THF. The solution was stirred for 1 h followed by the addition of 1g of ammonium chloride. The resulting colorless reaction mixture was warmed to r.t., transferred to a separatory funnel, diluted with 50 mL of water and extracted with dichloromethane (3x50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give a yellowish oil. The residue was purified by a column chromatography (elution with 60% EtOAc in hexanes, followed by elution with 2% Et_3N in EtOAc) to give 500 mg (66%) of the pure amine.

Example 554G

N-(Bis-(o-tolyl)methyl) bromoacetamide

The compound of Example 554F (100 mg, 0.47 mmol) was dissolved in 2 mL of 1,2-dichloroethane. To this solution at -78 °C was added Et_3N (0.05 mL) and then dropwise bromoacetyl bromide (40 mL, 0.47 mmol in 1 mL of 1,2-dichloroethane). The reaction mixture was stirred at -78 °C for 10 min, then at r.t. for 2 h., diluted with water (10 mL), and extracted with 1,2-dichloroethane (2x25mL). The combined organic layers were concentrated to give the bromoacetamide as a white solid (184 mg, 96%) suitable for further use without additional purification.

Example 554H

Ethyl *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-((bis-(o-tolyl)methyl)amino)carbonylmethyl)-pyrrolidine-3-carboxylate

The compound of Example 554G was dissolved in 5 mL of CH_3CN and added to a solution of 0.20 g (0.54 mmol) of the compound of Example 1E, *N,N*-diisopropylethylamine (0.1 mL) and CH_3CN (10 mL). The reaction mixture was stirred overnight at r.t., diluted with H_2O (25 mL) and extracted with EtOAc (2x25 mL). The combined organic fractions were

concentrated to give a yellow oil, which was purified by a column chromatography (elution with 40% of EtOAc in Hexanes) to give 250 mg (73%) of the title compound.

Example 554J

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-((bis-(o-tolyl)methyl)amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid

The compound of Example 554H was dissolved in a solution of 50 mL of ethanol and 10 mL of aqueous sodium hydroxide (6N) and stirred overnight at room temperature. The solution was then diluted with 30 mL of water, transferred to a separatory funnel and extracted with a mixture of 20% Hexanes in EtOAc (2x50mL). The aqueous phase was treated with hydrochloric acid (3N) until *pH*=4 and extracted with chloroform (3x50mL). The combined organic fractions containing the acid product were concentrated to get a yellow viscous oil. The title compound was then isolated by lyophylization from dilute CH_3CN/TFA/H_2O as an amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.20 (s, 3H), 3.02-3.33 (m, 2H), 3.40-3.72 (m, 3H), 3.80 (s, 3H), 4.16-4.24 (broad s, 1H), 5.92 (m, 2H), 6.36-6.42 (m, 1H), 6.58-6.67 (m, 2H), 6.81 (t, *J* = 9 Hz, 4H), 6.88-7.00 (m, 2H), 7.05-7.27 (m, 8H). MS (ESI+) m/e 593 ($M+H^+$). Anal. Calc for $C_{36}H_{36}N_2O_6$* 0.4 TFA: C, 69.25 H, 5.75 N, 4.39. Found: C, 69.20 H, 5.68 N, 4.22.

Example 555

trans,trans-2-[4-(2-Methoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(N-(2,2-dimethyl-1-phenylpropyl)-1-amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by using the procedures of Example 554, substituting 2,2-dimethyl-1-phenylpropan-1-one for 2,2'-dimethylbenzophenone in Example 554F and ethyl [4-(2-methoxyethoxy)benzoyl] acetate for ethyl (4-methoxybenzoyl) acetate in Example 1C . ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 9H, minor diastereomer), 0.88 (s, 9H, major diastereomer), 3.44 (s, 2H), 3.10-3.42 (m, 3H), 3.46 (s, 3H), 3.51-3.75 (m, 4H), 4.06-4.13 (m, 2H), 4.72 (m, 1H), 5.97 (m, 2H), 6.77 -7.45 (m, 12H). MS (ESI+) m/e 589 ($M+H^+$). Anal. Calc for $C_{34}H_{40}N_2O_7$* 0.75 TFA: C, 63.24 H, 6.09 N, 4.15. Found: C, 63.33 H, 6.18 N, 4.05.

Example 556

trans,trans-2-[4-(2-Methoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(N-((bis-(o-tolyl)methyl)amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by using the procedures of Example 554, substituting ethyl [4-(2-methoxyethoxy)benzoyl] acetate for ethyl (4-methoxybenzoyl) acetate in Example 554C . ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.20 (s, 3H), 2.94-3.23 (m,

3H), 3.32-3.51 (m, 2H), 3.47 (s, 3H), 3.58-3.69 (broad s, 1H), 3.76 (dd, J = 6, 1.5 Hz, 4H), 4.09 (t, J = 4.5 Hz, 1H), 5.93 (m, 2H), 6.34-6.41 (d, J = 7.5 Hz, 2H), 6.58 (broad s, 2H), 6.72-6.98 (m, 3H), 7.05-7.28 (m, 8H). MS (ESI+) m/e 637 ($M+H^+$). Anal. Calc for $C_{38}H_{40}N_2O_7$* 0.2 TFA: C, 69.93 H, 6.14 N, 4.25. Found: C, 70.03 H, 6.08 N, 4.21.

Example 557

trans,trans-2-[4-(2-Isopropoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(N-(2,2-dimethyl-1-phenylpropyl)-1-amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by using the procedures of Example 554, substituting 2,2-dimethyl-1-phenylpropan-1-one for 2,2'-dimethylbenzophenone in Example 554F and ethyl [4-(2-isopropoxyethoxy)benzoyl] acetate for ethyl (4-methoxybenzoyl) acetate in Example 1C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (s, 9H, major diastereomer), 0.88 (s, 9H, minor diastereomer), 1.19 (d, J = 7 Hz, 6H), 3.14-3.83 (m, 9H), 4.07 (p, J = 10.5, 4.5 Hz, 2H), 4.27-4.47 (m, 1H), 4.70 (t, J = 9 Hz, 1H), 5.93-6.00 (m, 2H), 6.73-7.38 (m, 12H). MS (ESI+) m/e 617 ($M+H^+$). Anal. Calc for $C_{36}H_{44}N_2O_7$* 0.6 TFA: C, 65.21 H, 6.56 N, 4.09. Found: C, 65.15 H, 6.59 N, 4.01.

Example 558

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(3,3-dimethyl-1-phenylbutyl)-1-amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared according to the procedures of Example 554, substituting 3,3-dimethyl-1-phenylbutan-1-one (prepared from commercially available 3,3-dimethyl-butyryl chloride according to the procedure in *J. Amer. Chem. Soc.*, **72**, 1950, 222-227) for 2,2'-dimethylbenzophenone in Example 554F. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (s, 9H, minor diastereomer), 0.89 (s, 9H, major diastereomer), 1.68 (t, J = 7.5 Hz, 2H), 3.05-3.30 (m, 2H), 3.34-3.53 (m, 2H), 3.62-2.74 (m, 1H), 3.77 (s, 2H), 3.80 (s, 3H), 4.92-5.02 (m, 1H), 5.97-6.01(m, 2H), 6.77 (t, J = 6 Hz, 2H), 6.88 (q, J = 18, 7.5 Hz, 2H), 6.97 (d, J = 6 Hz, 1H), 7.10-7.40 (m, 7H). MS (ESI+) m/e 559 ($M+H^+$). Anal. Calc for $C_{33}H_{38}N_2O_6$* 0.45 TFA: C, 66.75 H, 6.35 N, 4.59. Found: C, 66.69 H, 6.32 N, 4.46.

Example 559

trans,trans-2-[4-(2-Isopropopoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(N-((1-(o-tolyl)-1-(o-ethylphenyl)-methyl)amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by using the procedures of Example 554, substituting ethyl [4-(2-isopropoxyethoxy)benzoyl] acetate for ethyl (4-methoxybenzoyl) acetate in Example 554C and 2-ethyl-2'-methylbenzophenone (prepared from commercially available methyl-2-methylbenzoate according to the procedure in *J. Chem. Soc.*, 1929, 1631)

for 2,2'-dimethylbenzophenone in Example 554F. ^{1}H NMR (300 MHz, $CDCl_3$) δ1.04-1.28 (m, 9H) 2.20 (s, 3H), 2.53 (broad s, 2H), 2.94-3.23 (m, 3H), 3.35-3.87 (m, 6H), 4.08 (broad s, 3H), 4.52 (broad s, 1H), 5.96 (s, 2H), 6.48-7.35 (m, 15H). MS (ESI+) m/e 678 ($M+H^+$). Anal. Calc for $C_{41}H_{46}N_2O_7$* 0.95 TFA: C, 65.46 H, 6.01 N, 3.46. Found: C, 65.47 H, 6.00 N, 3.10.

Example 560

trans,trans-2-(4-(2-(2-Propoxy)ethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1- N-phenyl-N-t-butylhydrazino carbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 560A

N-phenyl-t-butylamine

t-Butylamine(2.0 eq.) was stirred in dry THF at r.t. and n-butyllithium(1.2 eq.) was added slowly. The resulting mixture was stirred for 30min. and then bromobenzene(1.0 eq.) added, refluxed for 4 hr. After work-up, it was purified and separated by a column(silica) to elute with hexane and ethyl acetate(9:1). Yield 50%.

Example 560B

Phenyl-t-butylnitrosoamine

Phenyl-t-butylamine (6g, 0.04mol) was treated with conc.HCl (5ml) and a solution of $NaNO_2$(6.4g, 2.4eq.) in 20ml of water was added slowly. The resulting mixture was stirred for 2hr at r.t. to produce an oily layer which was extracted with EtOAc, washed with brine, and dried over Na_2SO_4.Yield 6g (85%). This nitrosoamine was used for the next step without further purification.

Example 560C

N-phenyl-t-butylhydrazine

To a stirred suspension of zinc dust(5.14g, 0.079mol) in water(15ml) was added dropwise a solution of the compound of Example 560B (3.5g, 0.02mol) in acetic acid(9ml) and the resultant mixture was stirred for 1hr at r.t. Dichloromethane(20ml) was added, the mixture was adjusted to pH 8-9 with 15% NaOH, The zinc dust was removed by filtration, and the crude reaction mixture was extracted with dichloromethane. The combined organic layers were dried($MgSO_4$). Yield 1.97g(60%).

Example 560D

N-phenyl,N-t-butyl-N'-(bromoacetyl) hydrazine

The title compound was prepared by the procedure described Example 554G, substituting the compound of Example 560C.

Example 560E

trans,trans-2-(4-(2-(2-Propoxy)ethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-phenyl-N-t-butylhydrazino carbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 554. ^{1}H NMR (300MHz, DMSO) δ 0.92(d, J=24Hz, 6H), 1.10(s, 9H), 2.59-2.80(m, 2H), 2.95-3.10(m, 1H), 3.25-3.51(m, 3H), 3.58-3.70(m, 3H), 3.73-3.88(m, 1H), 4.02-4.07(m, 2H), 5.97-6.0(m, 2H), 6.78-6.93(m, 4H), 7.02-7.26(m, 7H), 7.35(d, J=8Hz, 1H). MS(ESI+) m/e 618(M+H+). Anal. Calc for C35H43N3O7.0.5H2O: C, 67.07 H, 7.08 N, 6.70. Found: C, 67.21 H, 6.61 N, 6.40.

Example 561

trans,trans-2-(4-(2-Methoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-phenyl-N-t-butylhydrazino carbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 554 and 560. ^{1}H NMR (300MHz, CD_3OD) δ 1.22(s, 9H), 2.87(d, J=15Hz, 1H), 2.98-3.07(m, 2H), 3.27(bs, 1H), 3.42(s, 3H), 3.60-368(m, 2H), 3.72-3.76(m, 2H), 3.92(d, J=9Hz, 1H), 4.10-4.14(m, 2H), 5.95(dd, J=2Hz,4Hz, 2H), 6.82(d, J=8Hz, 1H), 6.90(dd, J=2Hz, 9Hz, 1H), 7.96(d, J=8Hz, 2H), 7.07(d, J=2Hz, 1H), 7.10-7.23(m, 5H), 7.42(d, J=8Hz, 2H). MS (ESI+) m/e590 ($M+H^+$). Anal. Calc for $C_{33}H_{39}N_3O_7$.1.0 AcOH: C, 64.70, H, 6.67, N, 6.47. Found: C, 64.40, H, 6.40, N, 6.70.

As an indication that the compounds described herein act through binding to endothelin receptors, the compounds have been evaluated for their ability to displace endothelin from its receptor.

As an indication that the compounds described herein act through binding to endothelin receptors, the compounds have been evaluated for their ability to displace endothelin from its receptor.

Binding Assay
ET_A Receptor

Preparation of membranes from MMQ cells:

MMQ (MacLeod/MacQueen/Login cell line (prolactin secreting rat pituitary cells)) cells from 150 mL culture flasks were collected by centrifugation (1000xg for 10 min) and then homogenized in 25 mL of 10 mM Hepes (pH 7.4) containing 0.25 M sucrose and protease inhibitors (3 mM EDTA , 0.1 mM PMSF, and 5 μg/mL Pepstatin A) by a micro ultrasonic cell disruptor (Kontes). The mixture was centrifuged at 1000xg for 10 min. The supernatant was collected and centrifuged at 60,000xg for 60 min. The precipitate was resuspended in 20 mM Tris, pH 7.4 containing the above protease inhibitors and centrifuged again. The final pellet was resuspended in 20 mM Tris, pH 7.4 containing protease inhibitors and stored at -80°C until used. Protein content was determined by the Bio-Rad dye-binding protein assay.

(^{125}I)ET-1 binding to membranes:

Binding assays were performed in 96-well microtiter plates pretreated with 0.1% BSA. Membranes prepared from cells were diluted ~100 fold in Buffer B (20 mM Tris, 100 mM NaCl, 10 mM $MgCl_2$, pH 7.4, with 0.2% BSA, 0.1 mM PMSF, 5 μg/mL Pepstatin A, 0.025% bacitracin, and 3 mM EDTA) to a final concentration of 0.2 mg/mL of protein. In competition studies, membranes (0.02 mg) were incubated with 0.1 nM of (^{125}I)ET-1 in Buffer B (final volume: 0.2 mL) in the presence of increasing concentrations of unlabeled ET-1 or a test compound for 4 hours at 25 °C. After incubation, unbound ligands were separated from bound ligands by a vacuum filtration method using glass-fiber filter strips in PHD cell harvesters (Cambridge Technology, Inc., MA), followed by washing the filter strips with saline (1 mL) for three times. Nonspecific binding was determined in the presence of 1 μM ET-1, The data are shown in Table 4. The per cent inhibition at a concentration of 1 mM is shown. The data show that the compounds of the invention bind to the endothelin receptor.

Table 4
Binding Data

Example	% Inhibition of ET_A at 1 μM	Example	% Inhibition of ET_A at 1 μM
1D	96.4	34	95.5
2	58.4	35	91.8
3	42.2	36	94.5
4	78.2	37	47.9
5	95.1	38	100.0
6B	34.9	39	83.6
7	63.4	40	94.8
8	53.7	41	89.9
9	69.2	42	95.2
10	66.1	43	99.2
14	86.6	44	91.3
15	84.8	45	85.4
16	96.0	46	90.4
17	73.9	47	95.1
18	97.3	48	96.3
19A	90.3	52	84.0
20	80.9	54	64.6
21	56.3	55	50.5
22	86.3	56	34.3
23	85.9	57	93.2
26	83.0	58	81.9
27	61.2	59	70.8
28	63.8	60	42.8
29	85.3	61C	90.6
30	80.0	62	94.1
31B	93.6	63	92.0

Example	% Inhibition of ET_A at 1 μM	Example	% Inhibition of ET_A at 1 μM
64	95.0	98	86.8
65	82.8	99	92.1

66	87.7	100	76.8
67	96.3	101	89.2
68	84.6	102	75.2
69D	37.4	103	69.0
70	62.7	104	98.0
71	81.4	105	98.6
72C	80.7	106	90.0
73C	96.3	107	97.2
74	95.6	109	96.8
75C	95.3	110	94.4
76	93.1	111	101.8
79	100.4	112	94.9
80	89.4	113	94.3
82	90.3	114	86.2
83	85.0	115	88.4
84	65.3	116	79.3
86	52.6	117	95.2
87	62.4	118	93.2
88	84.3	119	86.6
89	84.6	120	99.5
91C	91.6	121	98.6
92C	107.4	122	95.3
93C	59.2	125	97.2
95D	82.1	126	91.7
96	86.1	127	91.4
97	89.0	128	95.4

Example	% Inhibition of ET_A at 1 μM	Example	% Inhibition of ET_A at 1 μM
123	89.7	156	92.6
124	91.0	157	83.8
129	100.1	158	91.8
130	91.0	159	36.2
131	89.5	160B	80.3
132	90.0	161	93.6
133	88.6	162B	91.5
134	92.2	163	90.6
135B	77.7	164	98.6
136	79.4	165	54.1
138	83.0	166	91.6
139	98.6	167	94.4
140	106.3	291	100.0
141	92.8	293	89.8
142B	78.7	294	77.7
143	20.6	295	93.0
144	78.2	296	87.1
145	32.4	297	84.4
146	25.0	298	93.3
147	73.0	299	90.4
148	94.7	300	96.1
149	84.6	301	96.7
150	93.6	302	86.6
151	80.5	303	87.2
152	86.9	304	89.7
153	97.1	305	87.4
154	80.2	306	93.3
155	92.7	307	92.2

Example	% Inhibition of ET_A at 1 μM	Example	% Inhibition of ET_A at 1 μM
308	93.0	351	99.0
309	80.7	352	96.2
310	87.1	353	73.7
311	92.3	354	79.3
312	88.2	355	100
313	96.3	356	93.5
314	86.0	357	96.3
315	82.7	358	62.7
316	74.0	359	94.7
317	68.5	360	93.7
318	79.0	361	92.8
319	79.0	362	94.1
320	82.2	363	82.3
322	95.6	365	59.2
323	91.3	366	91.5
324	95.0	367	71.0
334	88.0	368	94.6
335	84.1	370	84.3
340	94.0	371	97.2
341	87.4	372	91.6
342	89.9	373	92.9
343	98.7	374	91.4
344	95.6	375	97.8
345	86.6	376	90.2
346	88.9	377	85.6
348	91.3	378	91.1
349	73.0	379	90.7
350	92.1	380	99.0

Example	% Inhibition of ET_A at 1 μM	Example	% Inhibition of ET_A at 1 μM
381	95.7	408	100
382	96.8	409	89.4
383	91.4	410	91.4
384	79.4	411	93.5
385	86.2	412	86.4
386	47.8	413	99.5
387	98.7	414	91.4
388	69.2	415	87.3
389	100	416	86.4
390	98.2	417	98.7
391	45.6	418	100
392	93.7	420	100
393	100	421	100
394	97.8	422	96.6
395	79.8	423	89.1
396	98.7	424	85.8
397	100	425	90.8
398	90.0	426	97.2
399	59.9	427	100
400	93.0	428	100
401	96.5	429	100
402	80.5	430	94.1
403	96.1	431	99.1
404	95.4	432	95.5
405	86.4	433	99.6
406	94.5	434	100
407	100	435	97.8

Example	% Inhibition of ET_A at 1 μM	Example	% Inhibition of ET_A at 1 μM
436	100	459	97.4
437	100	460	91.6
438	94.3	461	99.6
439	94.3	462	98.3
440	100	463	96.1
441	98.3	464	97.1
442	100	465	95.1
443	100	466	94.2
444	100	467	93.6
445	98.1	468	88.7
446	97.8	469	98.7
447	96.9	470	100
448	97.4	471	100
449	100.0	475	91.6
450	99.7	476	82.3
451	100	477	80.1
452	100	479	96.5
453	94.4	495	95.9
454	96.8	496	92.7
455	99.1	497	83.7
456	95.3	498	81.6
457	88.9	499	68.5
458	93.4	500	55.7

Example.	% Inhibition of ET_A at 1 μM
502	95.7
503	97.0
504	97.1
505	95.8
506	99.7
507	99.3
508	97.6
509	100
510	100
511	99.2
512	98.9
513	98.0
514	100
515	99.1
516	99.7
517	94.1
518	96.3
519	99.1
520	97.4
521	100
523	99.0
524	99.2
525	100
526	100
527	96.6
528	98.3
529	98.1
531	99.8
532	100
533	97.9
536	100
537	97.2
554	58.2
555	66.7

556	24
557	72.2
558	79.8
559	5.8
560	0
561	0

As further demonstration of the efficacy of the described compounds as functional antagonists of endothelin, the ability of the described compounds to inhibit ET-1-induced phosphatidylinositol hydrolysis was measured.

Determination of Phosphatidylinositol (PI) Hydrolysis

MMQ cells (0.4 x 10^6 cells/mL) were labeled with 10 μCi/mL of (^{3}H)myo-inositol in RPMI for 16 hours. The cells were washed with PBS, then incubated with Buffer A containing protease inhibitors and 10 mM LiCl for 60 minutes. The cells were then incubated with test compounds for 5 minutes, and then challenged with 1 nM ET-1. ET-1 challenge was terminated by the addition of 1.5 mL of 1:2 (v/v) chloroform-methanol. Total inositol phosphates were extracted after adding chloroform and water to give final proportions of 1:1:0.9 (v/v/v) chloroform-methanol-water as described by Berridge (Biochem. J. 206 587-595 (1982)). The upper aqueous phase (1 mL) was retained and a small portion (100 μL) was counted. The rest of the aqueous sample was analyzed by batch chromatography using anion-exchange resin AG1-X8 (Bio-Rad). The IC_{50} is the concentration of test compound required to inhibit the ET-induced increase in PI turnover by 50%. The results of the above study clearly indicate that the compounds act as functional ET antagonists.

Table 5
Phosphatidylinositol Hydrolysis

Example	IC50 μM
1D	0.025
14	0.017
15	0.010
16	0.009
18	0.009
19	0.024
30	0.001
31B	0.002
43	0.0001
46	0.002
47	0.0005
48	0.0004
291	0.0098
300	0.0012
534	0.05
553	0.0004

Table 6
ET_A/ET_B Selectivity

MMQ cells, porcine cerebellar tissues (known to contain ET_B receptors) and chinese hamster ovary cells (CHO) permanently transfected with the human ETA or ETB receptor were homogenized in 25 ml of 10 mM Hepes (pH 7.4) containing 0.25 M sucrose and a protease inhibitor (50 mM EDTA, 0.1 mM

PMSF, 5 μg/ml Pepstatin A, and 0.025% Bacitracin) using a micro ultrasonic cell disruptor. The mixture was centrifuged at 1000xg for 10 min. The supernatant was collected and centrifuged at 60,000xg for 60 min. The precipitate was resuspended in 20 mM Tris, pH 7.4 containing protease inhibitor and centrifuged again. The final membrane pellet was resuspended in 20 mM Tris, pH 7.4 containing protease inhibitors and stored at -80 °C until used. Protein content was determined by the Bio-Rad dye-binding protein assay.

Binding assays were performed in 96-well microtiter plates pretreated with 0.1% BSA. Membranes prepared from cells were diluted ~100 fold in Buffer B (20 mM Tris, 100 mM NaCl, 10 mM $MgCl_2$, pH 7.4, with 0.2% BSA, 0.1 mM PMSF, 5 μg/mL Pepstatin A, 0.025% bacitracin, and 50 mM EDTA) to a final concentration of 0.2 mg/mL of protein. In competition binding studies, membranes (0.02 mg) were incubated with 0.1 nM of (125I)ET-1 (for ETA assay in MMQ or CHO cells transfected with human ET_A receptor) or (125I)ET-3 (for ETB assay in porcine cerebellum or CHO cells transfected with human ET_B receptor) in Buffer B (final volume: 0.2 mL) in the presence of increasing concentrations of the test compound for 3 hours at 25 °C. After incubation, unbound ligands were separated from bound ligands by a vacuum filtration method using glass-fiber filter strips in PHD cell harvesters (Cambridge Technology, Inc., MA), washing the filter strips three times with saline (1 mL). Nonspecific binding was determined in the presence of 1 μM ET-1. IC50 values are calculated using an average of at least two separate determinations. The data shows the selectivity of the compounds of the invention in binding to the endothelin receptors.

Table 6

EXAMPLE NO.	rET-A (%I @ 1μM)	rET-A IC_{50} (nM)	pET-B IC_{50} (nM)	Selectivity (rA/pB ratio)	hET-A IC_{50} (nM)	hET-B IC_{50} (nM)	Selectivity (hA/hB ratio)
502	95.7	3.0	71,000	23,000			
503	97.0	1.4	50,000	35,000	0.92	52,000	56,000
504	97.1	3.1	>100,000	>32,000	4.6	>100,000	>21,000

505	95.8	2.0	60,000	30,000	5.7	68,000	12,000
506	99.7	3.2	>100,000	>31,000	3.0	61,000	20,000
507	99.3	3.0	>100,000	>33,000	1.63	>100,000	>60,000
508	97.6	1.9	45,000	23,000	2.1	51,000	24,000
509	100	0.56	30,000	53,000	0.51	23,000	45,000
510	100	0.50	35,000	68,000	1.0	11,000	11,000
511	99.2	0.81	N.D.	----	0.60	15,000	25,000
512	98.9	0.42	>80,000	>190,000	0.58	60,000	>102,000
513	98.0	0.30	8,800	29,000	0.36	14,000	37,000
514	100	1.0	26,000	26,000	0.36	9,800	29,000
515	99.1	1.6	>62,000	>37,000	6.7	>100,000	>15,000
516	99.7	0.71	29,000	40,000	1.8	37,000	21,000
517	94.1	1.0	30,000	30,000	0.43	12,000	29,000
518	96.3	1.3	85,000	63,000	0.31	38,000	124,000
519	99.1	0.38	14,000	36,000	0.23	19,000	83,000
520	97.4	0.20	28,000	130,000			
521	100	0.67	37,000	54,000			
523	99.0	0.42	360	880	0.33	290	880

524	99.2	0.79	1,700	2,100	0.82	890	1,100
525	100	8.2	560	70			
526	100	42	---	---	17	7,400	440
527	96.6	7.9	10,000	1,300			
528	98.3	11	43,000	3,800			
529	98.1	3.6	6,300	1,700			
531	99.8	1.2	---	---	0.71	870	1,200
532	100	5.1	3,200	630			
533	97.9	76	7,900	100	40	22,000	560
534		0.12	0.36	3.0	0.08	0.28	3.5
536	100	0.52	17,000	33,000	0.92	52,000	56,000
537	97.2	0.96	5,900	6,200	0.23	1,900	8,200
552	97.3	0.78	7100,000	7125,000	1.0	>96,000	>96,000
553	100	0.26	42,400	160,000	0.29	39,500	136,000

Determination of Plasma Protein Binding

A stock solution of the test compound in 50% ethanol (2 mg/mL) was diluted 10X into PBS. A 0.4 mL sample of this secondary stock solution was added to 3.6 mL of fresh plasma, and incubated at room temperature for 1 hour. A 1 mL sample of this incubation mixture was transferred to a Centrifree ultrafiltration tube. The sample was centrifuged in a fixed-bucket rotor for approximately 2 min and the filtrate was discarded. The sample was

centrifuged for another 15-30 min. A 100 μL sample of the ultrafiltrate was transfered to a micro HPLC sample vial containing 150 ML of HPLC mobile phase and mixed thoroughly. A 50 μL sample was injected and the concentration of drug in the ultrafiltrate was determined by HPLC analysis compared against a standard sample prepared identically in the absence of plasma. Ultrafiltrate concentrations are calculated from a calibration curve. Protein binding is calculated according to the equation:

$$\%PB = (1-(Cu/Ci)) * 100\%$$

where Cu is the ultrafiltrate concentration and Ci is the initial plasma concentration. The percent of bound compound is listed in Table 7.

Table 7.

Example #43	$\geq$ 99.5 % bound
Example #530	78% bound
Example #531	92% bound
Example #532	96.8% bound
Example #533	82.6% bound

It has been demonstrated in the literature (Wu-Wong, et al., Life Sci. 1996, 58, 1839-1847, and references contained therein) that compounds which are highly protein bound show decreased potency *in vitro* in the presence of plasma proteins. A decrease in *in vitro* potency may correspondingly result in reduced *in vivo* potency. An endothelin antagonist which has reduced protein binding might be expected to be less susceptible to this effect, and thus be more potent as an *in vivo* agent.

The ability of " reduced protein binding" endothelin antagonists to exhibit enhanced activity in the presence of serum albumin has been demonstrated through the following study: A series of binding curves is recorded for a given antagonist, each experiment performed in the presence of increasing concentrations of serum albumin.

<u>Protocol for Albumin-induced binding shift studies</u>: Binding assays were performed in 96-well microtiter plates precoated with 0.1% BSA unless otherwise indicated. Membranes were diluted in Buffer B (20mM Tris, 100mM NaCl, 10mM MgCl2, pH 7.4, 0.1 mM PMSF, 5mg/mL Pepstatin A, 0.025%

bacitracin and 3 mM EDTA) to a final concentration of 0.05 mg/ml of protein. Varying concentrations of human serum albumin (HSA) were added as indicated. In competition studies, membranes were incubated with 0.1 nM of (^{125}I)ET in Buffer B (final volume: 0.2 ml) in the presence of increasing concentrations of unlabeled test ligands for 4 hours at 25°C. After incubation, unbound ligands were separated from bound ligands by vacuum filtration using glass-fiber filter strips in PHD cell harvesters (Cambridge Technology, Inc., Watertown, MA), followed by washing the filter strips with saline (1 ml) for three times. Nonspecific binding was determined in the presence of 1 μM ET-1.

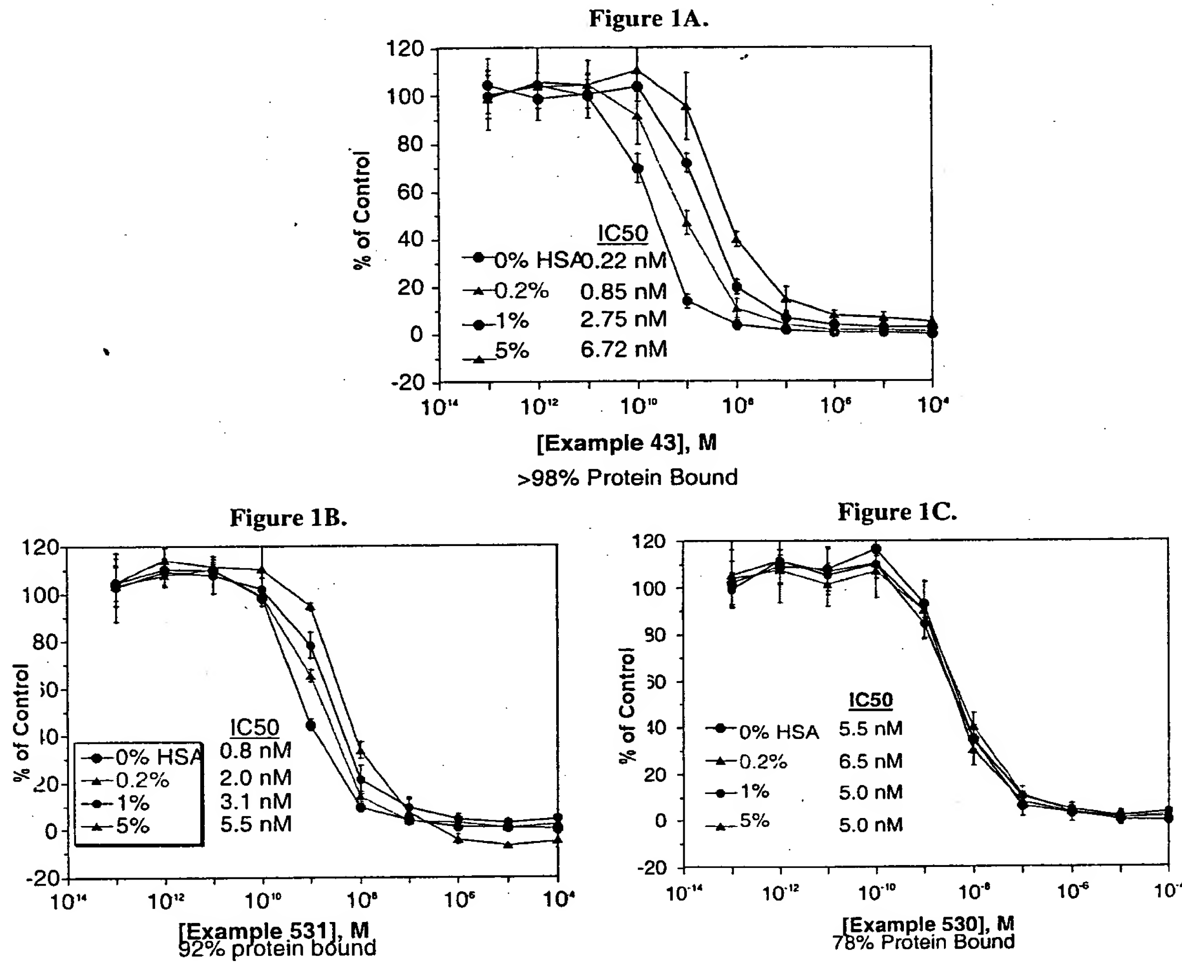


Figure 1

Inhibition of (^{125}I)ET-1 binding to human ET_A receptor by ET_A antagonists. Each curve was determined in the presence of either 0%, 0.2%, 1%, or 5% HSA, and assays were performed as described above. The results are expressed as % of

control binding, with ([125]I)ET-1 binding in the absence of antagonist defining 100%. Each point represents the mean (±S.D.) of three determinations.

As observed in Figure 1A, a compound which is highly protein bound (Example 43, >98% bound) shows a rightward shift of the binding curve (toward decreasing potency) in the presence of increasing albumin levels. The compound of Example 531 (Figure 1B), in which protein binding is reduced to 92%, shows a substantial diminution of this rightward shift; the shift is completely eliminated with the compound of Example 530 (Figure 1C), in which protein binding is reduced to 78%. This experiment demonstrates that a reduction in protein binding translates into increased potency in the presence of plasma proteins, and suggests that such compounds may exhibit enhanced *in vivo* activity.

The observed reduction in protein binding, in compounds which retain high affinity for endothelin receptors, appears linked to the placement of "basic" functionality (groups which carry a positive charge at physiological pH).

Such compounds also exhibit improved solubility in aqueous solutions, as demonstrated below (Table 1) in an experiment in which maximum solubility was measured in aqueous media at varying pH at about 25°C. These results indicate that compounds that contain charged groups on the amide sidechain exhibit increased solubility over a significant range of pH. Such increased aqueous solubility, coupled with the enhanced potency resulting from decreased protein binding, might make such compounds preferred for development as parenteral agents. Table 8 presents the pH-Solubility profiles for representative compounds of the present invention.

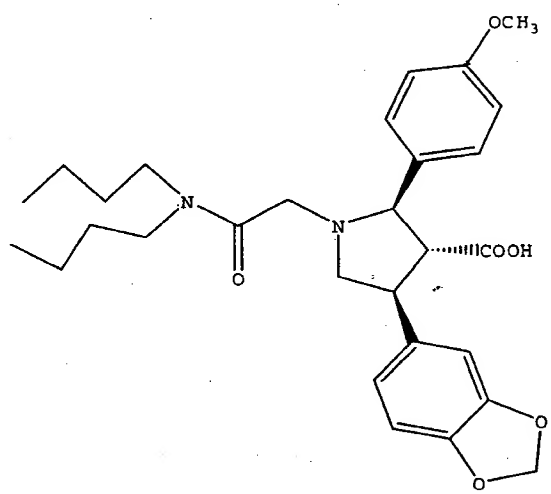
Table 8.

pH	(Example 43) (mg/r	(Example 531) (mg/ı
5.1	0.08	>3.3
6.5	0.51	>3.4
7.1	0.99	3.54
7.6	1.14	3.55

The present invention provides less protein bound compounds having improved *in vitro* and *in vivo* activity as pharmaceutical agents. The present invention also provides compounds that show that the affinity of hydrophobic acids for plasma protein may be reduced by attaching a counterbalanced

charge at a biologically acceptable site. For example, protein binding is reduced by attaching a "basic" functionality (groups which carry a positive charge at physiological pH) on the amide sidechain (see Formula XII wherein R_3 has an amide sidechain).

A particularly preferred compound of formula I is a compound of formula IIIa, also known as ABT-627:



IIIa

Other suitable endothelin ET-A receptor antagonist may be used, such as those disclosed in U.S. Patent Nos. 6,048,893, 6,017,951, and 5,998,468.

The term "inhibit" is defined to include its generally accepted meaning which includes preventing, prohibiting, restraining, and slowing, stopping or reversing progression, or severity, and holding in check and/or treating existing characteristics. The present method includes both medical therapeutic and/or prophylactic treatment, as appropriate.

The methods of the present invention are useful in men as well as in women. Preferably, however, the methods of the

present invention are useful in men, more preferably men with prostate cancer.

The ability of the compounds of the invention to treat cancers can be demonstrated according to the method described in J. Clin. Invest. 87 1867 (1991). Types of cancer includes primary cancer such as breast, prostate, lung, kidney, thyroid, myeloma, lymphoma, sarcoma, osteosarcoma, and ovarian.

The ability of the compounds of the invention to treat nociception can be demonstrated according to the method described in J. Pharmacol. Exp. Therap. 271 156 (1994).

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as

loweralkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

Basic addition salts can be prepared *in situ* during the final isolation and purification of the compounds of formula I, or separately by reacting the carboxylic acid function with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia, or an organic primary, secondary or tertiary amine. Such pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and

the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

The compounds of the invention are useful for antagonizing endothelin in humans or other mammals. Total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 1000 mg/kg body weight daily and more usually 0.1 to 100 mg/kg for oral administeration or 0.01 to 10 mg/kg for parenteral administeration. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

Pharmaceutical formulations may be prepared by procedures known in the art. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administeration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administeration, route of administeration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be administered orally, buccally, parenterally, sublingually, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administeration may also involve the use of transdermal administeration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, transcutaneous, intradermal, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleagenous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-propanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administeration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administeration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administeration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other

lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

A representative solid dosage form, for example, a tablet or a capsule, comprises:

Compound of the invention:	35% w/w
Starch, Pregelatinized, NF	50% w/w
Microcrystalline Cellulose, NF	10% w/w
Talc, Powder, USP	5% w/w

While the compounds of the invention can be administered as the sole active therapeutic agent, they can also be used in combination with one or more co-therapeutic agents, such as anticancer drugs or methods including, but not limited to, hormonal agents, such as leuprolide (Lupron®); gonadorelin antagonists, such as goserelin (Zoladex®) and abarelix; bicalutamide; nilutamide; flutamide; vitamin D; vitamin D

analogues; estrogen and estrogen analogues, such as diethylstibestrol; prednisone; hydrocortisone; ketoconazole; cyproterone acetate; progesterone; 5-alpha reductase inhibitors, such as finasteride; bone-seeking radionuclides, such as samarium (Quadramet®), strontium (Metastron®), and ^{186}rhenium; external beam radiation, including three dimensional conformal radiation; brachytherapy, which is the implantation of radioactive seeds directly into the prostate; monoclonal antibodies such as trastuzumab (Herceptin®); anti-angiogenic agents such as thrombospondin peptide or kringle 5; matrix metalloproteinase inhibitors; farnesyl transferase inhibitors; lycopenes; urokinase; plasminogen activator inhibitors; plasminogen activator receptor blockers; apoptosis inducers; selective and non-selective alpha blockers; platinum agents, such as cis-platinum and carbo-platinum; taxane class agents, such as docitaxil and paclitaxil; estramustine; gemcytabine; adriamycin; doxorubicin; daunorubicin; mitoxantrone; vinblastine; vincristine; capecitabine; irinotecan; topotecan;

5-fluorouracil; interferons; cytoxan; methotrexate; cytokines, such as IL-2; PPAR agonists, such as thiazolidine diones; retinoid-type agents, 5-lipooxygenase inhibitors, such as zyfo (Zilueton®), COX-2 inhibitors; gene-therapy based therapeutics, including sense and anti-sense genes; cholesterol lowering drugs, such as lovastatin, pravastatin, and

simvistatin; bisphosphonates; osteoprotegrin; and antibodies, both monoclonal and polyclonal; antibody-coupled radionucleotides; antibody-coupled cytotoxic agents; antibody-coupled radionucleotides; viral-vector delivered agents; vaccines directed at protein, carbohydrate, or nucleic acid targets; aminoglutethimide; and suramin.

These combinations can be administered as separate compositions or as a single dosage form containing both or all agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions, which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

In addition, the compounds invention can be used in combination with one or more co-therapeutic agents which impede net bone loss, such as estrogens, bisphosphonates, and estrogen receptor modulators, such as raloxifene, and calcitonin.

The compounds of the invention can additionally be administered in combination with surgery, such as radical prostatectomy, cryotherapy, transurethral resection of the prostate as an adjuvant, and the like, or prior to surgery as a neoadjuvant agent.

The current major diseases or conditions of bone which are of public concern include, but are not limited to, post-menopausal osteoporosis, ovariectomy patients, senile osteoporosis, patients undergoing long-term treatment of

corticosteroids, side effects from glucocorticoid or steroid treatment, patients suffering from Cushings's syndrome, gonadal dysgenesis, periarticular erosions in rheumatoid arthritis, osteoarthritis, Paget's disease, osteohalisteresis, osteomalacia, hypercalcemia of malignancy, osteopenia due to bone metastases, periodontal disease, hyperparathyroidism, osteroperosis from Lupron therapy, and starvation. All of these conditions are characterized by bone loss, resulting from an imbalance between the degradation of bone (bone resorption) and the formation of new healthy bone. This turnover of bone continues normally throughout life and is the mechanism by which bone regenerates. However, the conditions stated above will tip the balance towards bone loss such that the amount of bone resorbed is inadequately replaced with new bone, resulting in net bone loss.

Examples

Studies were performed on male subjects with asymptomatic hormone refractory prostate cancer with rising PSA levels and on male subjects with symptomatic hormone refractory prostate cancer with rising PSA levels and pain. Subjects in the phase II studies had castrate levels of testosterone, either due to pharmacologic intervention, via leuprolide (Lupron®) or goserelin (Zoladex®), or via surgical castration. Subjects

received ABT-627 or placebo. The following tests were conducted:

ABT-627 was formulated in 2.5 and 10 mg doses. An oral liquid formulation of ABT-627 was also prepared as follows: 1 mg/ml ABT-627, 50% glycerin, 14% alcohol, and water. Matching placebos were also provided.

A number of recognized or putative biochemical markers of disease progression have been used to monitor treatment of individuals with prostate cancer. Among these markers are serum Prostate Specific Antigen (PSA), serum acid Phosphatase, Interleukin-6, and Chromagranin-A. As currently accepted, favorable treatment is marked by a decrease or slower rate of increase for PSA, acid phosphatase, and Interleukin-6, while a favorable response is marked by an increase in Chromagranin-A.

Serum samples were obtained from subjects during treatment with the ET antagonist ABT-627 in order to determine PSA, acid phosphatase, IL-6, and Chromagranin-A values.

Prostate Specific Antigen Level Assay

The effect of ABT-627 administeration on prostate specific antigen (PSA) levels in human subject serum samples was determined using the procedure described in the Chiron Diagnostics ACS: Centaur PSA2 Assay. This assay is a two-site sandwich immunoassay which uses direct chemiluminescense and constant amounts of two antibodies. The first antibody, the

Lite Reagent, is an affinity purified polyclonal sheep anti-PSA antibody labeled with acridinium ester. The Lite Reagent is purchased as a 5.0 mL reagent pack comprising the polyclonal sheep anti-PSA antibody (3.1 μg) in buffered saline with sodium azide (0.1%). The second antibody, the Solid Phase, is a monoclonal mouse anti-PSA antibody covalently coupled to paramagnetic particles. The Solid Phase is purchased as a 25.0 mL reagent pack comprising the covalently coupled monoclonal mouse anti-PSA antibody (316 μg) in buffered saline with sodium azide (0.1%). The assay was performed at Quintiles Laboratories (Smyrna, GA) using Chiron Diagnostics ACS: Centaur® Automated Chemiluminescence Systems.

Briefly, a subject population was treated with a placebo or 2.5 mg or 10 mg of ABT-627. Blood samples were collected, allowed to adequately clot, centrifuged at 1000 x g for 15-20 minutes, and stored at -20 °C if not assayed within 48 hours. A cuvette was charged sequentially with serum, Lite Reagent (50 μL), and Solid Phase (250 μL). The resulting mixture was incubated for 7.5 minutes at 37 °C, separated, and treated with the solution of Acid Reagent and Base Reagent to initiate the chemiluminescent reaction. A direct relationship exists between the amount of PSA present in the patient sample and the RLU's (relative light units) detected. As shown by the area under the curve (AUC) in Figure 2, the rate of increase of PSA

in the serum samples decreases after the adminsteration of ABT-627, demonstrating the effectivness of ABT-627 as an agent for treating prostate cancer.

Acid Phosphatase Levels

The effect of ABT-627 administeration on Acid Phosphatase levels in human subject serum samples was determined at Quintiles Laboratories using the chemical test described in Sigma Diagnostics Acid Phosphatase (ACP) Procedure No. 435. The enzyme Acid Phosphatase (ACP) catalyzes the hydrolysis of alpha-naphthyl phosphate to alpha-naphthol and inorganic phosphate. The alpha-naphthol immediately reacts with fast red TR salt to produce a yellow chromophore with an absorbance maximum at 405 nm. The rate of increase in absorbance at 405 nm is directly proportional to ACP activity in the sample. ACP activity was determined in the presence and absence of L-tartrate, the difference being attributed to prostatic acid phosphatase activity.

Briefly, a subject population was treated with a placebo or 2.5 mg or 10 mg of ABT-627. Blood samples were collected, allowed to adequately clot, centrifuged at 1000 x g for 15-20 minutes, and stored at -20 °C if not assayed within 48 hours. Assays were performed on a Hitachi Spectrophotomer. A cuvette was charged sequentially with ACP reagent (1 mL), prepared as described in the assay protocol, and serum (0.1 mL). The

mixture was agitated and incubated for 5 minutes, and an absorbance (A) at 405 nm (versus water as a reference) was read to provide an initial absorbance. The mixture was incubated for another 5 minutes, and a second absorbance was read to provide a final absorbance. A change A/5 minute value was obtained by subtracting the initial absorbance from the final absorbance and was used to calculate total ACP activity.

To provide the tartrate-resistant acid phosphatase activity, the above procedure was repeated with the addition of ACP tartrate reagent (0.01 mL) to the cuvette containing the ACP reagent and mixing before adding the serum. Prostatic acid phosphatase activity was calculated by subtracting the the tartrate-resistant acid phosphatase activity from the ACP activity. As shown shown by the (AUC) in Figure 7, the rate of increase and the average change from baseline for acid phosphatase was decreased in those subjects treated with ABT-627, again demonstrating the effectivness of ABT-627 as an agent for treating prostate cancer.

Chromagranin-A Levels

The effect of ABT-627 adminstration on Chromagranin-A levels in human serum samples was determined by proprietary assay conducted at the Nichols Institute. The procedure is a two site chemiluminescence assay (ICMA) using one monoclonal

antibody conjugated with biotin, another monoclonal antibody labeled with an acridinium ester, and an avidin-coated solid phase. The antibody/Chromagranin-A/antibody complex is bound to the solid phase by the avidin-biotin interaction and unbound materials are removed by washing. The bound, acridinium-labeled material produces light that is detected in a luminometer after addition of triggering agents. The Limit of Detection (LOD) for the assay was 0.07 ng/mL. As shown by the AUC in Figure 8, the average change from baseline for Chromagranin-A was higher for subjects treated with 2.5 mg/day of ABT-627, again demonstrating the effectivness of ABT-627 as an agent for treating prostate cancer.

Interleukin-6 Levels

The effect of ABT-627 adminstration on Interleukin-6 levels in human serum samples was determined at Quintiles Laboratories using a sandwich immunoassay. Human serum samples and standards were incubated in microtiter plate wells coated with a monoclonal anti-IL-6 antibody, in the presence of a second monoclonal anti IL-6 antibody, linked to acetylcholinesterase. After incubation, the wells were washed, and the bound enzymatic activity was measured using a chromogenic substrate. The intensity of the color was proportional to the concentration of IL-6 in the sample or standard. As shown by the AUC Figure 1, the average change in

baseline for Interleukin-6 was lower in those subjects treated with ABT-627, demonstrating the effectivness of ABT-627 as an agent for reducing inflammation and ameliorating pain.

Bone Scan Methodology

Bone scans were performed with an NDA approved, Tc-99m phosphonate type radiopharmaceutical. This technique uses whole body format (skull to feet) so that anterior and posterior images are presented when using a 510 K-approved gamma camera. Alternatively, spot views covering both anterior and posterior projections of the total body can be obtained. Interpretation was performed according to standard nuclear medicine criteria, on a bone by bone basis, by recording the number of lesions at each site. Each site was evaluated against a confidence score of 1 to 5, where 1 is negative, 2 is probably negative, 3 is equivocal, 4 is probably positive, and 5 is definitely positive. The MSKCC (Clin. Can. Res. 1998; **4**:1765-1772) was used to record these findings. For the purposes of scoring the extent of disease or the response to treatment, lesions with a confidence score of 4 and 5 were considered positive, and all other lesions were considered negative. In addition, in a blinded study, a reference nuclear medicine physician interpreted the bone scans quantitatively as follows: the percent of involved bone was estimated for each individual bone, and the individual bone involvement was summed

to calculate a global percent bone scan index (BSI). More specifically, the bone scan was separated into three indices. The first was the appindicular scan which involved arms and legs (i.e. the humorous and all bones distal to the humerous and the femur and everything distal to the femur). The second was the axial (everything but the arms and the legs). The results of these scans were combined to provide the total BSI.

Bone scans were conducted on each subject on day one of the study, and on the final day of the study, and the changes from baseline in bone scan index scores were analysed by mean change and mean percent change, adjusting for baseline characteristics as co-variates using SAS version XXX software.

As shown in Figure 6, bone scans indicated a decrease in the proportion of total skeketal involvement in those subjects receiving ABT-627 versus placebo, demonstrating the effectivness of ABT-627 as an agent for reducing the fraction of total skeletal involvement by tumor.

VAS Methodology/Administeration/Analysis

The Visual Analog Scale (VAS) is a common instrument of pain assessment performed by having a subject draw a vertical line on a 10 cm scale at the point that best describes his or her pain on average in the last 24 hours. A diagram of the scale is shown below:

No pain I-----------------------I Pain as bad as it could possibly be

(not to scale)

During the course of the study, pain asessments were done daily, at bedtime, by the subject. If the subject was unable to maintain the log, a caregiver could complete the log on his or her behalf. The log also contained a table on which was recorded all daily pain medication consumed by the patient. The logs of daily VAS scores and analgesic consumption were collected at biweekly visits of the subject to the clinic when a new log was distributed. Clinical personnel who received the logs measured the score by measuring the distance (in mm) from the "no pain" end mark to the point where the subject's line crossed the VAS line. The number was written into the case report form next to the date the subject completed that page of the logbook.

Subjects with pain were initially stabilized in their pain so that their pain was treated to a tolerable and constant level. For this study, "tolerable and constant" refers to a pain score less than or equal to 5 cm on the VAS for an average of seven successive days while using four or less rescue doses of pain medication per day. A rescue medication dose refers to a dose equal to one single dose a patient used for common timed pain relief.

The weekly VAS scores were calculated excluding the lowest and highest score for each week and averaging the remaining

five scores. If there were two days with the same VAS score, the day with the highest analgesic use was discarded.

The weekly mean VAS score was used to define subjects as responders or non-responders. A subject was considered a responder based on the reduction in the pain intensity: a weekly VAS score reduction of greater than or equal to 25% during at least two consecutive weeks without an increase of analgesic use during the same period (compared to baseline). Alternatively, a subject was considered a responder if his pain analgesic consumption was reduced by at least 25% during at least two consecutive weeks without a concomitant increase in VAS score.

The percentage of responders in each treatment group was compared to evaluate drug efficacy. The comparison was subjected to an adjustment for baseline characteristics and prognostic factors as co-variates, and the analysis was performed using the Cochran-Mantel-Haenszel test or a generalized linear model.

Weekly VAS scores are examined using a longitudinal analysis method to explore trends over time. The duration of the response, defined as the time from baseline to the last weekly assessment for which the responder definition was satisfied, was analyzed using the Kaplan-Meier methodology and logrank test. Cox proportional hazard models were used as needed (see U.S. Department of Health and Human Services.

Management of Cancer Pain Clinical Practice Guidelines. AHCPR Publication #94-0592, Rockville, MD (1994). As shown by the AUC in Figure 3, VAS scores showed a decrease in pain, independent of the effects of morphine, after treatment with with ABT-627, demonstrating the effectivness of ABT-627 as an agent for ameliorating pain.

Osteoblastic Activity and Bone Markers

Markers of osteoblastic activity were assessed using urine samples. Bone markers include bone alkaline phosphatase (BAP), deoxypridinoline, and N-telopeptide of Type I collagen. Blood samples were collected prior to dosing on Day 1, Day 42, Day 84, Day 168, and every 28 days after Day 168, with a final collection on the last day of the study.

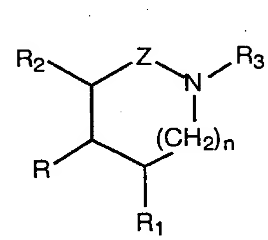
Bone Alkaline Phosphatase

Bone Alkaline Phosphatase levels were determined using the bone-specific Alkphase-B® assay published by Metra Biosystems (Mountain View, CA). As shown by the AUC in Figure 5, BAP levels decreased in subjects treated with ABT-627, demonstrating the effectivness of ABT-627 as an agent for inhibiting abnormal bone remodeling.

Crosslinked N-Telopeptide Levels:

Cross-linked N-telopeptide levels were determined using the DiaSorin (Stillwater, MN) assay for the quantitative determination of carboxyterminal cross-linked telopeptide of type I collagen (ICTP) in human serum by equilibrium radioimmunoassay (RIA). Briefly, samples were incubated with the ^{125}I ICTP tracer and ICTP primary antibody for 2 hours at 37 °C. Following the 2 hour incubation, a pre-precipitated second antibody complex was added to separate the bound from free tracer. The assay was then centrifuged and decanted after a 30 minute incubation at room temperature. The bound tracer in the pellet was counted with a gamma counter. Counts were inversely proportional to the amount of ICTP present in each sample. As shown by the AUC in Figure 4, Crosslinked N-telopeptide levels decreased in subjects treated with ABT-627, demonstrating the effectivness of ABT-627 as an agent for inhibiting the bone remodeling associated with bone diseases.

The present invention covers compounds having the formula XII:



XII

wherein

Z is -C(R_{18})(R_{19})- or -C(O)- wherein R_{18} and R_{19} are independently selected from hydrogen and loweralkyl;

n is 0 or 1;

R is -$(CH_2)_m$-W wherein m is an integer from 0 to 6 and W is

(a) -$C(O)_2$-G wherein G is hydrogen or a carboxy protecting group,

(b) -PO_3H_2,

(c) -P(O)(OH)E wherein E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) -C(O)NHR_{17} wherein R_{17} is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

(h) tetrazolyl,

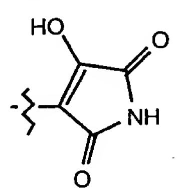
(i) hydroxy,

(j) alkoxy,

(k) sulfonamido,

(l) -C(O)NHS$(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl, aryl or dialkylamino,

(m) -$S(O)_2$NHC(O)R_{16} wherein R_{16} is defined as above,

(n) 

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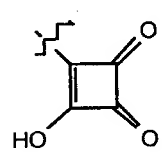
(o) 

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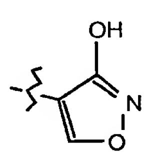
(p) 

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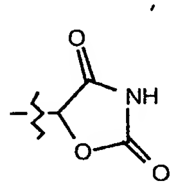
(q) 

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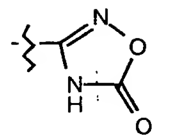
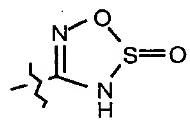
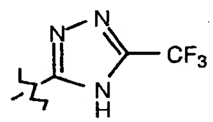
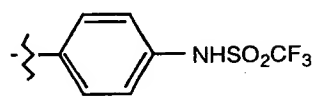
(r)  ,

(s)  ,

(t)  , or

(u)  ;

R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N$-R_{cc}- wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R_1 and R_2 is other than hydrogen;

R_3 is (a)R_4-C(O)-R_5-, R_4-C(O)-R_5- N(R_6)- ,

wherein R_5 is (i) a covalent bond, (ii) alkylene, (iii) alkenylene, (iv) -N(R_{20})-R_8- or -R_{8a}-N(R_{20})-R_8- wherein R_8 and R_{8a} are independently selected from the group consisting of alkylene and alkenylene and R_{20} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl or cycloalkylalkyl or (v) -O-R_9- or -R_{9a}-O-R_9- wherein R_9 and R_{9a} are independently selected from alkylene;

R_4 and R_6 are $(R_{11})(R_{12})N$- wherein R_{11} and R_{12} are independently selected from

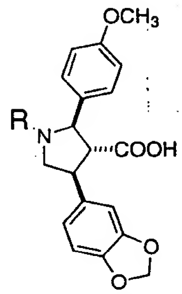
(1) hydrogen,
(2) loweralkyl,
(3) haloalkyl,
(4) alkoxyalkyl,

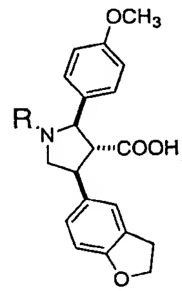
(5) haloalkoxyalkyl,
(6) alkenyl,
(7) alkynyl,
(8) cycloalkyl,
(9) cycloalkylalkyl,
(10) aryl,
(11) heterocyclic,
(12) arylalkyl,
(13) (heterocyclic)alkyl,
(14) hydroxyalkyl,
(15) alkoxy,
(16) aminoalkyl,
(17) trialkylaminoalkyl,
(18) alkylaminoalkyl,
(19) dialkylaminoalkyl,
(20) carboxyalkyl,
(21) (cycloalkyl)aminoalkyl,
(22) (cycloalkyl)alkylaminoalkyl,
(23) (heterocyclic)aminoalkyl, and
(24) (heterocyclic)aminoalkyl, with the proviso that at least one of R_{11} and R_{12} is selected from heterocyclic, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, trialkylaminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, (cycloalkyl)aminoalkyl, (cycloalkyl)alkylaminoalkyl, (heterocyclic)aminoalkyl, and (heterocyclic)alkylaminoalkyl;

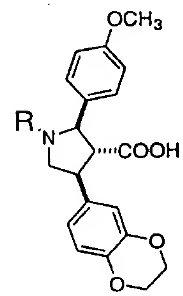
or a pharmaceutically acceptable salt thereof.

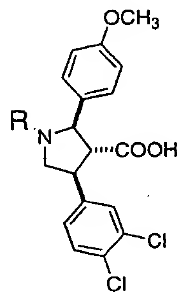
Preferred compounds having reduced protein binding are shown in Table 9A wherein R may be selected from the substituents shown in Table 9B.

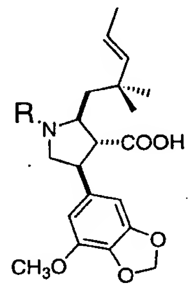
Table 9A.

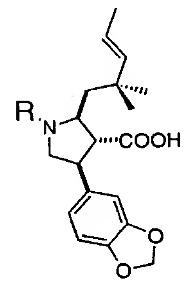
1 

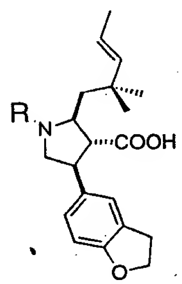
2 

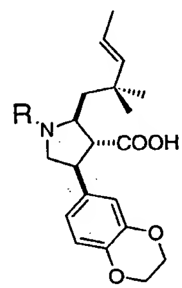
3 

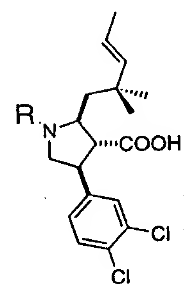
4 

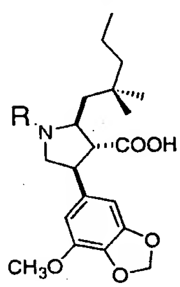
5 

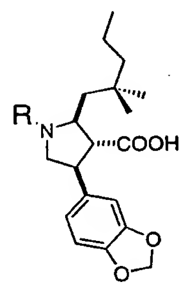
6 

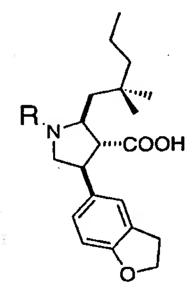
7 

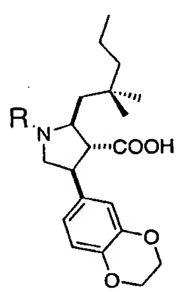
8 

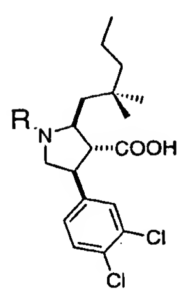
9 

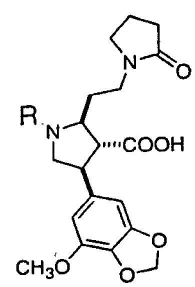
10 

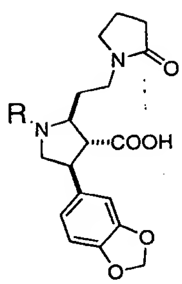
11 

12 

13 

14 

15 



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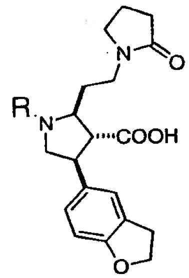

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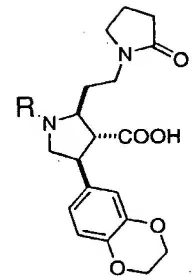

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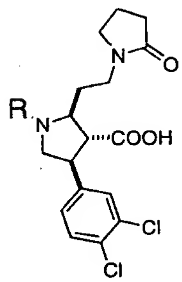

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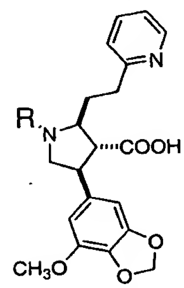

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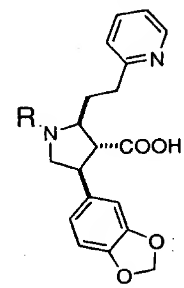

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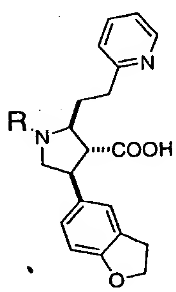

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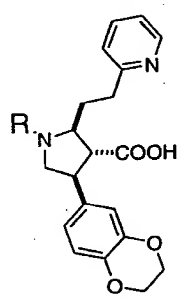

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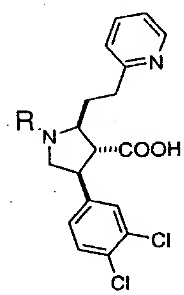

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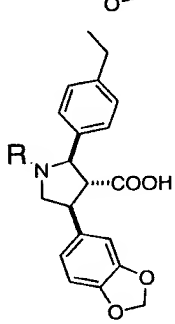

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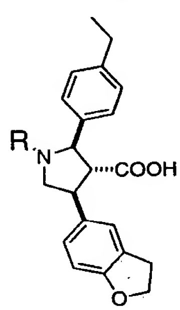

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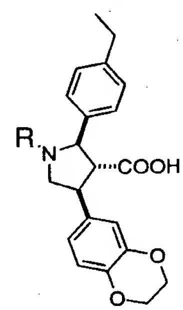

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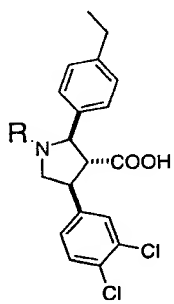

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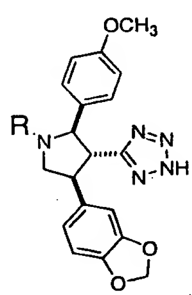

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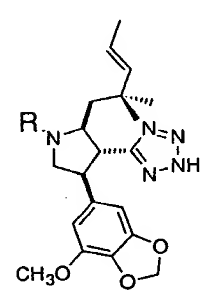

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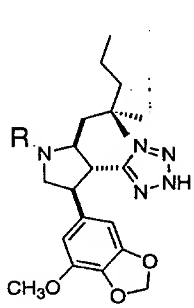
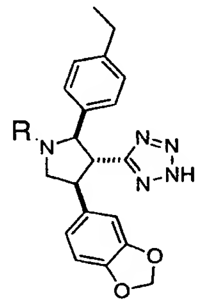
31 

32 

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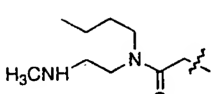
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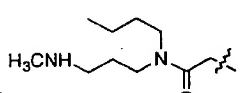
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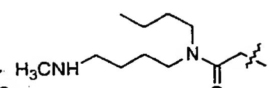
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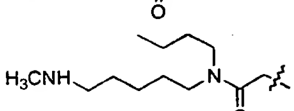
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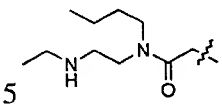
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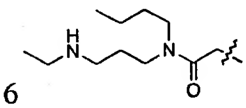
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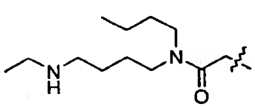
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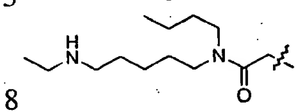
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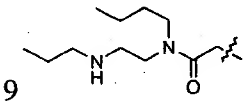
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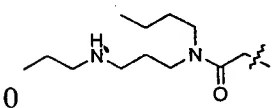
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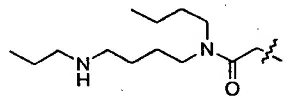
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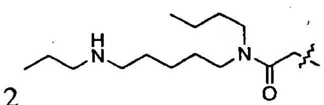
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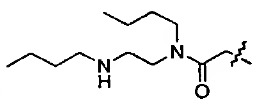
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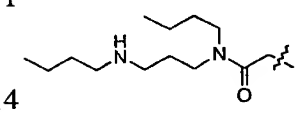
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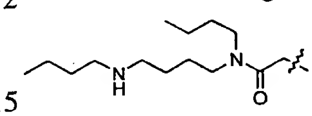
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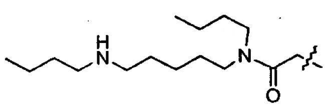
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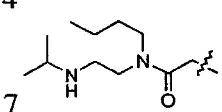
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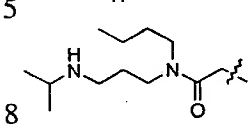
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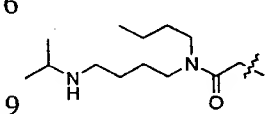
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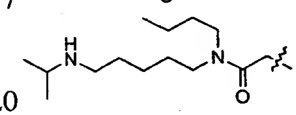
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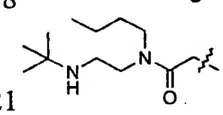
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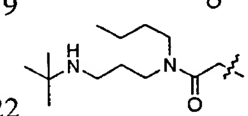
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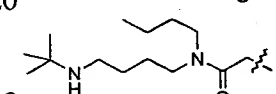
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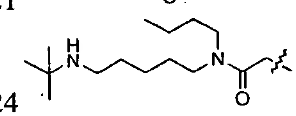
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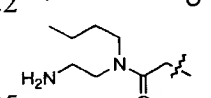
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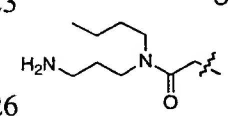
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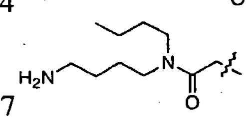
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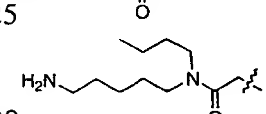
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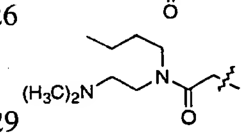
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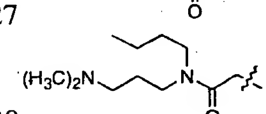
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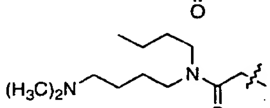
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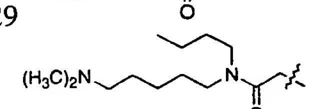
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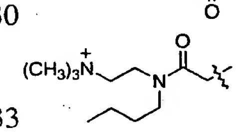
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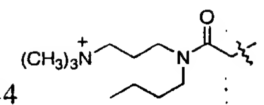
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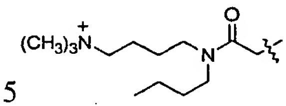
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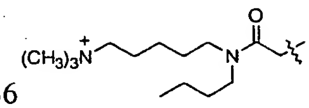
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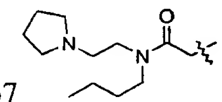
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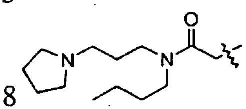
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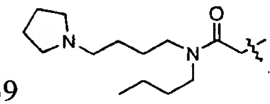
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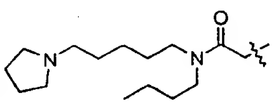
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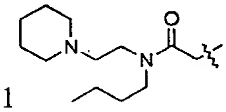
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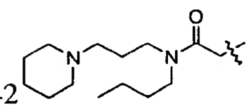
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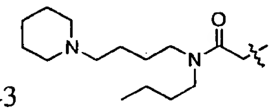
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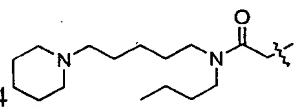
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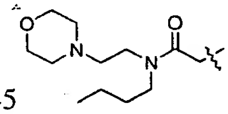
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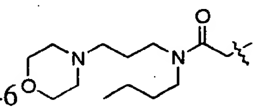
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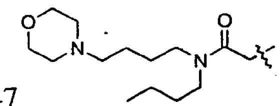
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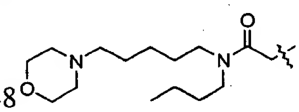
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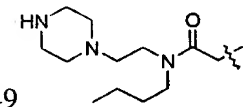
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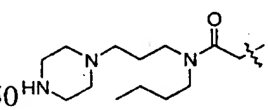
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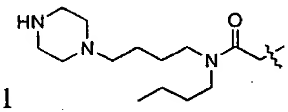
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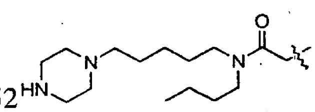
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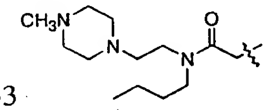
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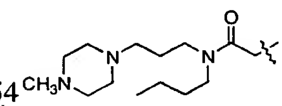
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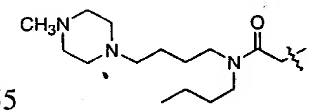
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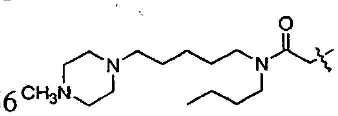
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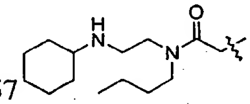
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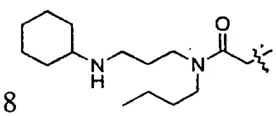
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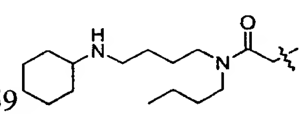
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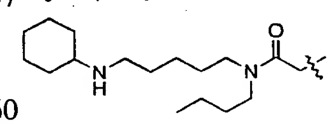
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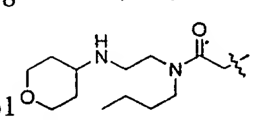
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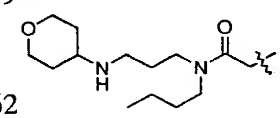
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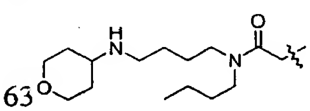
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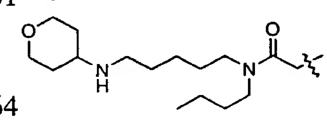
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For the purposes of this disclosure, the term "(cycloalkyl)aminoalkyl" as used herein refers a cycloalkyl moiety attached to the parent compound through an aminoalkyl. Examples of (cycloalkyl)aminoalkyl include (cyclohexane)aminopropyl, (cyclohexane)aminoethyl, and the like.

The term "(heterocyclic)aminoalkyl" as used herein refers to a heterocyclic moiety attached to the parent compound through an aminoalkyl. Examples of (heterocyclic)aminoalkyl include (pyridine)aminopropyl, (benzofuran)aminopropyl, (tetrahydopyran)aminoethyl, and the like.

The term "(cycloalkyl)alkylaminoalkyl" refers to a cycloalkyl moiety attached to the parent compound through an alkylaminoalkyl. Examples of (cycloalkyl)alkylaminoalkyl include (cyclohexane)ethylaminomethyl, (cyclopentane)methylaminoisopropyl, and the like.

The term "(heterocyclic)alkylaminoalkyl" as used herein refers to a heterocyclic moiety attached to the parent compound through an alkylaminoalkyl. Examples of (heterocyclic)alkylaminoalkyl include (pyridine)ethylaminopropyl, (benzofuran)methylaminoisobutyl, (tetrahydopyran)methylaminoethyl, and the like.

The ability of the compounds of the invention to lower blood pressure can be demonstrated according to the methods described in Matsumura, et al., Eur. J. Pharmacol. 185 103 (1990) and Takata, et al., Clin. Exp. Pharmacol. Physiol. 10 131 (1983).

The ability of the compounds of the invention to treat congestive heart failure can be demonstrated according to the method described in Margulies, et al., Circulation 82 2226 (1990).

The ability of the compounds of the invention to treat myocardial ischemia can be demonstrated according to the method described in Watanabe, et al., Nature 344 114 (1990).

The ability of the compounds of the invention to treat coronary angina can be demonstrated according to the method described in Heistad, et al., Circ. Res. 54 711 (1984).

The ability of the compounds of the invention to treat cerebral vasospasm can be demonstrated according to the methods described in Nakagomi, et al., J. Neurosurg. 66 915 (1987) or Matsumura, et al., Life Sci. 49 841-848 (1991).

The ability of the compounds of the invention to treat cerebral ischemia can be demonstrated according to the method described in Hara et al., European. J. Pharmacol. 197: 75-82, (1991).

The ability of the compounds of the invention to treat acute renal failure can be demonstrated according to the method described in Kon, et al., J. Clin. Invest. 83 1762 (1989).

The ability of the compounds of the invention to treat chronic renal failure can be demonstrated according to the method described in Benigni, et al., Kidney Int. 44 440-444 (1993).

The ability of the compounds of the invention to treat gastric ulceration can be demonstrated according to the method described in Wallace, et al., Am. J. Physiol. 256 G661 (1989).

The ability of the compounds of the invention to treat cyclosporin-induced nephrotoxicity can be demonstrated according to the method described in Kon, et al., Kidney Int. 37 1487 (1990).

The ability of the compounds of the invention to treat endotoxin-induced toxicity (shock) can be demonstrated according to the method described in Takahashi, et al., Clinical Sci. 79 619 (1990).

The ability of the compounds of the invention to treat asthma can be demonstrated according to the method described in Potvin and Varma, Can. J. Physiol. and Pharmacol. 67 1213 (1989).

The ability of the compounds of the invention to treat transplant-induced atherosclerosis can be demonstrated according to the method described in Foegh, et al., Atherosclerosis 78 229-236 (1989).

The ability of the compounds of the invention to treat atherosclerosis can be demonstrated according to the methods described in Bobik, et al., Am. J. Physiol. 258 C408 (1990) and Chobanian, et al., Hypertension 15 327 (1990).

The ability of the compounds of the invention to treat LPL-related lipoprotein disorders can be demonstrated according to the method described in Ishida, et al., Biochem. Pharmacol. 44 1431-1436 (1992).

The ability of the compounds of the invention to treat proliferative diseases can be demonstrated according to the methods described in Bunchman ET and CA Brookshire, Transplantation Proceed. 23 967-968 (1991); Yamagishi, et al., Biochem. Biophys. Res. Comm. 191 840-846 (1993); and Shichiri, et al., J. Clin. Invest. 87 1867-1871 (1991). Proliferative diseases include smooth muscle proliferation, systemic sclerosis, cirrhosis of the liver, adult respiratory distress syndrome, idiopathic cardiomyopathy, lupus erythematosus, diabetic retinopathy or other retinopathies, psoriasis, scleroderma, prostatic hyperplasia, cardiac hyperplasia, restenosis following arterial injury or other pathologic stenosis of blood vessels.

The ability of the compounds of the invention to treat acute or chronic pulmonary hypertension can be demonstrated according to the method described in Bonvallet et al., Am. J. Physiol. 266 H1327 (1994). Pulmonary hypertension can be associated with congestive heart failure, mitral valve stenosis, emphysema, lung fibrosis, chronic obstructive pulmonary disease

(COPD), acute repiratory distress syndrome (ARDS), altitude sickness, chemical exposure, or may be idiopathic.

The ability of the compounds of the invention to treat plaletet aggregation, and thrombosis, can be demonstrated according to the method described in McMurdo et al. Eu. J. Pharmacol. 259 51 (1994).

The ability of the compounds of the invention to treat cancers can be demonstrated according to the method described in Shichiri, et al., J. Clin. Invest. 87 1867 (1991).

The ability of the compounds of the invention to treat IL-2 (and other cytokine) mediated cardiotoxicity and vascular permeability disorders can be demonstrated according to the method described in Klemm et al., Proc. Nat. Acad. Sci. 92 2691 (1995).

The ability of the compounds of the invention to treat nociception can be demonstrated according to the method described in Yamamoto et al., J. Pharmacol. Exp. Therap. 271 156 (1994).

The ability of the compounds of the invention to treat colitis can be demonstrated according to the method described in Hogaboam et al (EUR. J. Pharmacol. 1996, 309, 261-269).

The ability of the compounds of the invention to treat ischemia-repurfusion injury in kidney transplantation can be demonstrated according to the method described in Aktan et al (Transplant Int 1996, 9, 201-207).

The ability of the compounds of the invention to treat angina, pulmonary hypertension, raynaud's disease, and migraine can be demonstrated according to the method described in Ferro and Webb (Drugs 1996, 51,12-27).

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as

loweralkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

Basic addition salts can be prepared *in situ* during the final isolation and purification of the compounds of formula (I), or separately by reacting the carboxylic acid function with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia, or an organic primary, secondary or tertiary amine. Such pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

The compounds of the invention are useful for antagonizing endothelin in a human or other mammal. In addition, the compounds of the present invention are useful (in a human or other mammal) for the treatment of hypertension, acute or chronic pulmonary hypertension, Raynaud's disease, congestive heart failure, myocardial ischemia, reperfusion injury, coronary angina, cerebral ischemia, cerebral vasospasm, chronic or acute renal failure, non-steroidal antiinflammatory drug induced gastric ulceration, cyclosporin induced nephrotoxicity, endotoxin-induced toxicity, asthma, fibrotic or proliferative diseases, including smooth muscle proliferation, systemic sclerosis, cirrhosis of the liver, adult respiratory distress syndrome, idiopathic cardiomyopathy, lupus erythematosus, diabetic retinopathy or other retinopathies, psoriasis, scleroderma, prostatic hyperplasia, cardiac hyperplasia, restenosis following arterial injury or other pathologic stenosis of blood vessels, LPL-related lipoprotein disorders, transplantation-induced

atherosclerosis or atherosclerosis in general, platelet aggregation, thrombosis, cancers, prostate cancer, IL-2 and other cytokine mediated cardiotoxicity and permeability disorders, and nociception, especially treatment of bone pain associated with bone cancer.

Total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 1000 mg/kg body weight daily and more usually 0.1 to 100 mg/kg for oral administration or 0.01 to 10 mg/kg for parenteral administration. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be administered orally, parenterally, sublingually, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleagenous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-propanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically aceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

A representative solid dosage form, for example, a tablet or a capsule, comprises:

Compound of the invention:	35% w/w
Starch, Pregelatinized, NF	50% w/w
Microcrystalline Cellulose, NF	10% w/w

Talc, Powder, USP 5% w/w

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more cardiovascular agents independently selected from diuretics, adrenergic blocking agents, vasodilators, calcium channel blockers, renin inhibitors, angiotensin converting enzyme (ACE) inhibitors, angiotensin II antagonists, potassium channel activators and other cardiovascular agents.

Representative diuretics include hydrochlorothiazide, chlorothiazide, acetazolamide, amiloride, bumetanide, benzthiazide, ethacrynic acid, furosemide, indacrinone, metolazone, spironolactone, triamterene, chlorthalidone and the like or a pharmaceutically acceptable salt thereof.

Representative adrenergic blocking agents include phentolamine, phenoxybenzamine, prazosin, terazosin, tolazine, atenolol, metoprolol, nadolol, propranolol, timolol, carteolol and the like or a pharmaceutically acceptable salt thereof.

Representative vasodilators include hydralazine, minoxidil, diazoxide, nitroprusside and the like or a pharmaceutically acceptable salt thereof.

Representative calcium channel blockers include amrinone, bencyclane, diltiazem, fendiline, flunarizine, nicardipine, nimodipine, perhexilene, verapamil, gallopamil, nifedipine and the like or a pharmaceutically acceptable salt thereof.

Representative renin inhibitors include enalkiren, zankiren, RO 42-5892, PD-134672 and the like or a pharmaceutically acceptable salt thereof.

Representative angiotensin II antagonists include DUP 753, A-81988 and the like.

Representative ACE inhibitors include captopril, enalapril, lisinopril and the like or a pharmaceutically acceptable salt thereof.

Representative potassium channel activators include pinacidil and the like or a pharmaceutically acceptable salt thereof.

Other representative cardiovascular agents include sympatholytic agents such as methyldopa, clonidine, guanabenz, reserpine and the like or a pharmaceutically acceptable salt thereof.

The compounds of the invention and the cardiovascular agent can be administered at the recommended maximum clinical dosage or at lower doses. Dosage levels of the active compounds in the compositions of the invention may be varied so as to obtain a desired therapeutic response

depending on the route of administration, severity of the disease and the response of the patient. The combination can be administered as separate compositions or as a single dosage form containing both agents.

When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds, processes, compositions and methods. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.